

## (12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
20 January 2005 (20.01.2005)

PCT

(10) International Publication Number  
**WO 2005/005597 A2**

(51) International Patent Classification<sup>7</sup>: **C12N**

CA 94707 (US). HAYASHIZAKI, Yoshihide [—/—]; \*\*  
(\*\*). KAMIYA, Mamoru [—/—]; \*\* (\*\*).

(21) International Application Number:  
PCT/US2003/027106

(22) International Filing Date: 28 August 2003 (28.08.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/476,632 9 June 2003 (09.06.2003) US  
60/476,621 9 June 2003 (09.06.2003) US  
60/485,359 8 July 2003 (08.07.2003) US  
60/485,217 8 July 2003 (08.07.2003) US

(74) Agent: GARRETT, Arthur, S.; Finnegan, Henderson,  
Farnbow Garrett & Dunner, LLP, 1300 I Street, N.W.,  
Washington, DC 20005-3315 (US).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU,  
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,  
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,  
GM, HR, HU, ID, IL, IN, IS, JP, KG, KP, KR, KZ, LC,  
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,  
MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC,  
SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA,  
UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM,  
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),  
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,  
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,  
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,  
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

(71) Applicants (*for all designated States except US*): **FIVE  
PRIME THERAPEUTICS, INC.** [US/US]; 951 Gate-  
way Boulevard, South San Francisco, CA 94080 (US).  
**RIKEN** [JP/JP]; (The Institute of Physical and Chemical  
Research), 2-1, Hirosawa, Wako, Saitama, 351-0198 (JP).  
**KABUSHIKI KAISHA DAINIPON** [JP/JP]; 3-35, Miya  
1-chome, Minato-ku, Tokyo 108-0073 (JP).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **WILLIAMS,  
Lewis, T.** [US/US]; 125 Chapel Drive, Mill Valley, CA  
94941 (US). **CHU, Keting** [US/US]; 2017 Easton Drive,  
Burlingame, CA 94010 (US). **LEE, Ernestine** [US/US];  
226 Arlington Avenue, Kensington, CA 94707 (US). **HEN-  
TIR, Kevin** [US/US]; 226 Arlington Avenue, Kensington,

## Published:

— without international search report and to be republished  
upon receipt of that report

For two-letter codes and other abbreviations, refer to the "Guid-  
ance Notes on Codes and Abbreviations" appearing at the begin-  
ning of each regular issue of the PCT Gazette.

(54) Title: NOVEL MOUSE POLYPEPTIDES ENCODE BY POLYNUCLEOTIDES AND METHODS OF THEIR USE

(57) Abstract: The invention provides novel polynucleotides, related polypeptides, related nucleic acid and polypeptide composi-  
tions, and related modulators, such as antibodies and small molecule modulators. The invention also provides methods to make and  
use these polynucleotides, polypeptides, related compositions, and modulators. These methods include diagnostic, prophylactic and  
therapeutic applications. The compositions, and methods of the invention are useful in treating proliferative disorders, e.g., cancers,  
and inflammatory, immune, bacterial, and viral disorders.

WO 2005/005597 A2

# **NOVEL MOUSE POLYPEPTIDES ENCODED BY POLYNUCLEOTIDES AND METHODS OF THEIR USE**

## **PRIORITY CLAIM**

[001] This application is related to the following provisional applications filed in the United States Patent and Trademark Office, the disclosures of which are hereby incorporated by reference:

<b>Application Number</b>	<b>Title</b>	<b>Filing Date</b>
60/476,632	Novel Mouse Polynucleotides Relating to Kinases, Phosphatases, and Proteases	June 9, 2003
60/476,621	Methods of Use for Novel Mouse Polynucleotides Relating to Kinases, Phosphatases, and Proteases	June 9, 2003
60/485,539	Novel Mouse Polynucleotides Relating to Secreted and Transmembrane Proteins	July 8, 2003
60/485,217	Methods of Use for Novel Mouse Polynucleotides Relating to Secreted and Transmembrane Proteins	July 8, 2003

## **TECHNICAL FIELD**

[002] The present invention is related generally to novel polynucleotides and novel polypeptides encoded thereby, their compositions, antibodies directed thereto, and other agonists or antagonists thereto. The polynucleotides and polypeptides are useful in diagnostic, prophylactic, and therapeutic applications for a variety of diseases, disorders, syndromes and conditions, as well as in discovering new diagnostics, prophylactics, and therapeutics for such diseases, disorders, syndromes, and conditions (hereinafter disorders). The present invention also relates to methods of modulating biological activities through the use of the novel polynucleotides and novel polypeptides of the invention and through the use of agonists and antagonists, such as antibodies, thereto.

[003] This application further relates to the field of polypeptides that are associated with regulating cell growth and differentiation, that are over-expressed in cancer, and/or that can be associated with proliferation or inhibition of cancer growth, including hematopoietic cancers such as leukemias, lymphomas, and solid

cancers such as lung cancer, for example, adenocarcinomas and/or squamous cell carcinomas. These polypeptides may also be associated with other conditions, such as inflammatory, immune, and metabolic disorders, as well as microbial infections, including viral, bacterial, fungal, and parasitic diseases, disorders, syndromes, or conditions.

[004] This application further relates to modulators of biological activity that can specifically bind to these polynucleotides or polypeptides, or otherwise specifically modulate their activity. For example, they can directly or indirectly induce antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), endocytosis, apoptosis, or recruitment of other cells to effect cell activation, cell inactivation, cell growth or differentiation or inhibition thereof, and cell killing.

[005] The sequences of the invention encompass a variety of different types of nucleic acids and polypeptides with different structures and functions. They can encode or comprise polypeptides belonging to different protein families ("Pfam"). The "Pfam" system is an organization of protein sequence classification and analysis, based on conserved protein domains; it can be publicly accessed in a number of ways, for example, at <http://pfam.wustl.edu>. Protein domains are portions of proteins that have a tertiary structure and sometimes have enzymatic or binding activities; multiple domains can be connected by flexible polypeptide regions within a protein. Pfam domains can comprise the N-terminus or the C-terminus of a protein, or can be situated at any point in between. The Pfam system identifies protein families based on these domains and provides an annotated, searchable database that classifies proteins into families (Bateman et al., 2002).

[006] Sequences of the invention can encode or be comprised of more than one Pfam. Sequences encompassed by the invention include, but are not limited to, the polypeptide and polynucleotide sequences of the molecules shown in the Sequence Listing and corresponding molecular sequences found at all developmental stages of an organism. Sequences of the invention can comprise genes or gene segments designated by the Sequence Listing, and their gene products, i.e., RNA and polypeptides. They also include variants of those presented in the Sequence Listing that are present in the normal physiological state, e.g., variant alleles such as SNPs, splice variants, as well as variants that are affected in pathological states, such as disease-related mutations or sequences with alterations that lead to pathology, and

variants with conservative amino acid changes. Sequences of the invention are categorized below; any given sequence can belong to one or more than one category.

#### **Secreted Protein-Related Sequences**

[007] Secreted proteins, also referred to as secreted factors, include proteins that are produced by cells and exported extracellularly, extracellular fragments of transmembrane proteins that are proteolytically cleaved, and extracellular fragments of cell surface receptors, which fragments may be soluble. An example of a secreted protein is keratinocyte growth factor (KGF), which stimulates the growth of keratinocytes, and is useful for repairing tissue after chemotherapy or radiotherapy.

[008] Many and widely variant biological functions are mediated by a wide variety of different types of secreted proteins. Yet, despite the sequencing of the human genome, relatively few pharmaceutically useful secreted proteins have been identified. It would be advantageous to discover novel secreted proteins or polypeptides, and their corresponding polynucleotides that have medical utility.

[009] Pharmaceutically useful secreted proteins of the present invention will have in common the ability to act as ligands for binding to receptors on cell surfaces in ligand/receptor interactions, to trigger certain intracellular responses, such as inducing signal transduction to activate cells or inhibit cellular activity, to induce cellular growth, proliferation, or differentiation, or to induce the production of other factors that, in turn, mediate such activities.

[010] The cell types having cell surface receptors responsive to secreted proteins are various, including, for example, stem cells; progenitor cells; and precursor cells and mature cells of the hematopoietic, hepatic, neural, lung, heart, thymic, splenic, epithelial, pancreatic, adipose, gastrointestinal, colonic, optic, olfactory, bone and musculoskeletal lineages. Further, the hematopoietic cells can be red blood cells or white blood cells, including cells of the B lymphocytic (B cell), T lymphocytic (T cell), dendritic, megakaryocytic, natural killer (NK), macrophagic, eosinophilic, and basophilic lineages. The cell types responsive to secreted proteins also include normal cells or cells implicated in disease, disorders, syndromes, or other pathological conditions.

[011] As an example, certain of the secreted proteins of the present invention can stimulate T or B cell growth or differentiation by interacting with precursor T or B cells or hematopoietic progenitor cells, or bone marrow stem cells. As another example, certain secreted proteins of the present invention can maintain



stem cells, progenitor cells or precursor cells in an undifferentiated state. As a further example, certain secreted proteins of the present invention can regulate bone growth by stimulation or inhibition thereof, secretion of insulin, glucose metabolism, cell proliferation, response to microbial infection, and regeneration of tissues including neural, muscular, and epithelial. Moreover, certain secreted proteins of the present invention can induce apoptosis such as in cancer cells or inflammatory cells.

[012] Certain of the secreted proteins of the present invention are useful for diagnosis, prophylaxis, or treatment of disorders in subjects that are deficient in such secreted proteins or require regeneration of certain tissues, the proliferation of which is dependent on such secreted proteins, or requires an inhibition or activation of growth that is dependent on such secreted proteins. Examples of such disorders include cancer, such as bone cancer, brain tumors, breast and ovarian cancer, Burkitt's lymphoma, chronic myeloid leukemia, colon cancer, endocrine system cancers, gastrointestinal cancers, gynecological cancers, head and neck cancers, leukemia, lung cancer, lymphomas, malignant melanoma, metastases, multiple endocrine neoplasia, myelomas, neurofibromatosis, pancreatic cancer, pediatric cancers, penile cancer, prostate cancer, disorders related to the Ras oncogene, retinoblastoma (RB), sarcomas, skin cancers, testicular cancer, thyroid cancer, urinary tract cancers, and von Hippel-Lindau syndrome.

[013] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of hematopoiesis, including thrombosis; bleeding; anemias, e.g., iron deficiency and other hypoproliferative anemias, megaloblastic anemias, hemolytic anemias, acute blood loss, and aplastic anemia; hemoglobinopathies; disorders of granulocytes and monocytes; myelodysplasias and related bone marrow failure syndromes; polycythemias, e.g., polycythemia vera; acute and chronic myeloid leukemia, and other myeloproliferative diseases, e.g., malignancies of lymphoid cells; stimulation of replacement cell growth following irradiation or chemotherapy; and plasma cell disorders.

[014] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of hemostasis, such as disorders of the platelet and vessel wall, disorders of coagulation and thrombosis, and anticoagulant, fibrinolytic and antiplatelet therapies.

[015] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the cardiovascular system including

disorders of the heart, such as heart failure; congenital heart disease; rheumatic fever; cor pulmonale; cardiomyopathies e.g., myocarditis; pericardial disease; cardiac tumors; cardiac manifestations of systemic diseases; and vascular diseases, such as acute myocardial infarction, ischemic heart disease, hypertensive vascular disease, diseases of the aorta, and vascular diseases of the extremities.

[016] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the respiratory system, such as asthma, hypersensitivity pneumonitis, e.g., with pulmonary infiltration, pneumonia, necrotizing pulmonary infections, bronchiectasis, cystic fibrosis, chronic bronchitis, emphysema and airway obstruction, interstitial lung diseases, primary pulmonary hypertension, pulmonary thromboembolism, disorders of the pleura, mediastinum, and diaphragm, disorders of ventilation, sleep apnea, and acute respiratory distress syndrome.

[017] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the kidney and urinary tract, such as, for example, chronic renal failure and glomerulopathies.

[018] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the gastrointestinal system, including disorders of the alimentary tract, such as, for example, peptic ulcer disease and related disorders, inflammatory bowel disease, irritable bowel syndrome; disorders of the liver and biliary tract, such as, for example, hyperbilirubinemias, acute viral hepatitis, chronic hepatitis, and cirrhosis; and disorders of the pancreas, such as acute or chronic pancreatitis.

[019] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the immune system, connective tissue, and joints, including, for example, autoimmune diseases, primary immune deficiency diseases, human immunodeficiency virus diseases, allergies, systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjogren's syndrome, ankylosing spondylitis, reactive arthritis, vasculitis, sarcoidosis, amyloidosis, osteoarthritis, gout, psoriatic, and other arthritis.

[020] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the endocrine system, including, for example, disorders of the pituitary, hypothalamus, neurohypophysis, thyroid gland,

adrenal cortex, testes, ovary, and other organs of the female reproductive system, such as breast; as well as pheochromocytoma, diabetes mellitus, and hypoglycemia.

[021] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of bone and mineral metabolism, and other metabolic processes, including, for example, diseases of the parathyroid gland and other hyper- and hypocalcemic disorders, osteoporosis, Paget's disease and other dysplasia of bone, disorders of lipoprotein metabolism, hemochromatosis, porphyries, disorders of purine and pyrimidine metabolism, Wilson's disease, lysosomal storage diseases, glycogen storage diseases, lipodystrophies, and other primary disorders of adipose tissue.

[022] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the central nervous system, including, for example, seizures and epilepsy, cerebrovascular diseases, Alzheimer's disease and other extrapyramidal disorders, ataxic disorders, amyotrophic lateral sclerosis and other motor neuron diseases, disorders of the autonomic nervous system, diseases of the spinal cord, including spinal cord injury, primary and metastatic tumors of the nervous system, multiple sclerosis, and other demyelinating diseases, as well as chronic and recurrent meningitis.

[023] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of nerves or muscle, including, for example, Guillain-Barre Syndrome, myasthenia gravis and other diseases of the neuromuscular junction, polymyositis, dermatomyositis, muscular dystrophies, and other muscle diseases.

[024] Certain of the secreted proteins herein can be used for diagnosis, prophylaxis, and treatment of disorders of the skin, including, for example, eczema, psoriasis, cutaneous infections, acne, and other common skin disorders, and immunologically mediated skin diseases.

[025] The agonists or antagonists of the secreted proteins herein or fragments thereof can be useful in treating elevated levels of such proteins in ny of the disorders above, and including angina, anoxia, arrhythmias, asthma, atherosclerosis, benign prostatic hyperplasia, Buerger's Disease, cardiac arrest, cardiogenic shock, cerebral trauma, Crohn's Disease, congenital heart disease, mild congestive heart failure (CHF), severe congestive heart failure, cerebral ischemia, cerebral infarction, cerebral vasospasm, cirrhosis, diabetes, dilated cardiomyopathy, endotoxic shock,

gastric mucosal damage, glaucoma, head injury, hemodialysis, hemorrhagic shock, hypertension (essential), hypertension (malignant), hypertension (pulmonary), hypertension (e.g., pulmonary, after bypass), hypoglycemia, inflammatory arthritis, ischemic bowel disease, ischemic disease, male penile erectile dysfunction, malignant hemangioendothelioma, myocardial infarction, myocardial ischemia, prenatal asphyxia, postoperative cardiac surgery, prostate cancer, preeclampsia, Raynaud's Phenomenon, renal failure (acute), renal failure (chronic), renal ischemia, restenosis, sepsis syndrome, subarachnoid hemorrhage (acute), surgical operations, status epilepticus, stroke (thromboembolic), stroke (hemorrhagic), Takayasu's arteritis, ulcerative colitis, uremia after hemodialysis, and uremia before hemodialysis.

[026] Secreted proteins can be screened for functional activities in appropriate functional assays, as is conventional in the art. Such assays include, for example, *in vitro* and *in vivo* assays for factors that stimulate the proliferation or differentiation of stem cells, progenitor cells, or precursor cells into T cells, B cells, pancreatic islet cells, bone cells, neuronal cells, etc.

[027] The tetratricopeptide repeat (TPR) is an example of a protein domain characteristic of a protein family, and is present in some of the secreted polypeptides of the invention. The TPR family is characterized by a degenerate 34 amino acid sequence present in a wide variety of proteins; it mediates protein-protein interactions, and is involved in scaffold formation and the assembly of multiprotein complexes (<http://pfam.wustl.edu/cgi-bin/getdesc?name=TPR>). Secreted protein-related sequences can also possess or interact with cytochrome P450 domains, which are involved in the oxidative degradation of various compounds, including environmental toxins and mutagens (<http://pfam.wustl.edu/cgi-bin/getdesc?name=p450>). Secreted protein-related sequences, e.g., cholesteryl ester transfer protein and phospholipid transfer protein, can also possess or interact with the LBP/BPI/CETP domain, which is characteristically found in lipid-binding serum glycoproteins ([http://pfam.wustl.edu/cgi-bin/getdesc?name=LBP\\_BPI\\_CETP](http://pfam.wustl.edu/cgi-bin/getdesc?name=LBP_BPI_CETP)). Secreted protein-related sequences can also possess or interact with peptidase S8 domains, also known as subtilase domains, which are comprised of serine proteases with a wide range of peptidase activities, including exopeptidase, endopeptidase, oligopeptidase, and omega-peptidase activity ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Peptidase\\_S8](http://pfam.wustl.edu/cgi-bin/getdesc?name=Peptidase_S8)). Secreted protein-related sequences can also possess or interact with adh\_short, or short-chain dehydrogenase domains, which are found in a large family of proteins, and are made

up of short-chain dehydrogenases and reductase enzymes; most family members function as NAD- or NADP- dependent oxidoreductases ([http://pfam.wustl.edu/cgi-bin/getdesc?name=adh\\_short](http://pfam.wustl.edu/cgi-bin/getdesc?name=adh_short)).

[028] The inventors herein have identified novel secreted proteins using an algorithm that is constructed on the basis of a number of attributes including hydrophobicity, two-dimensional structure, prediction of signal sequence cleavage site, and other parameters. Based on such algorithm, a sequence that has a secreted tree vote of 0.5 – 1.0, preferably, 0.6 – 1.0, is believed to be a secreted protein.

#### **Transmembrane Protein-Related Sequences**

[029] Transmembrane proteins extend into or through the cell membrane's lipid bilayer; they can span the membrane once, or more than once. Transmembrane proteins that span the membrane once are "single transmembrane proteins" (STM), and transmembrane proteins that span the membrane more than once are "multiple transmembrane proteins" (MTM). Examples of transmembrane proteins include the insulin receptor, adenylate cyclase, and intestinal brush border esterase.

[030] A single transmembrane protein typically has one transmembrane (TM) domain, spanning a series of consecutive amino acid residues, numbered on the basis of distance from the N-terminus, with the first amino acid residue at the N-terminus as number 1. A multi-transmembrane protein typically has more than one TM domain, each spanning a series of consecutive amino acid residues, numbered in the same way as the STM protein.

[031] Transmembrane proteins, having part of their molecules on either side of the bilayers, have many and widely variant biological functions. They transport molecules, e.g., ions or proteins across membranes, transduce signals across membranes, act as receptors, and function as antigens. Transmembrane proteins are often involved in cell signaling events; they can comprise signaling molecules, or can interact with signaling molecules. For example, tyrosine kinases can be transmembrane receptor proteins. Abnormalities of receptor tyrosine kinases are associated with human cancers; tumor cells are known to use receptor tyrosine kinases in transduction pathways to achieve tumor growth, angiogenesis and metastasis. Therefore, receptor tyrosine kinases represent pivotal targets in cancer therapy. It would be similarly advantageous to discover novel transmembrane proteins or polypeptides, and their corresponding polynucleotides that have additional medical utility.

[032] The transmembrane polypeptides of the invention, like the secreted polypeptides, also have many different functional domains, and belong to a wide variety of Pfam families. Transmembrane protein-related sequences can possess or interact with immunoglobulin (ig) domains, which are characteristically found in the immunoglobulin superfamily, comprised of hundreds of proteins, with various functions (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ig>). Transmembrane protein-related sequences can also possess or interact with ion\_trans domains, which are polypeptides characterized by six transmembrane helices, and which transport ions across membranes ([http://pfam.wustl.edu/cgi-bin/getdesc?name=ion\\_trans](http://pfam.wustl.edu/cgi-bin/getdesc?name=ion_trans)). Proteins in this family can demonstrate specificity for particular ions, e.g., sodium, potassium, and calcium. Transmembrane protein-related sequences can also possess or interact with integrase core domains, which mediate the integration of a DNA copy of a viral genome into a host chromosome; e.g., HIV integrase catalyses the incorporation of virally derived DNA into the human genome, presenting a target for the development of new therapeutics for the treatment of AIDS (<http://pfam.wustl.edu/cgi-bin/getdesc?name=rvc>). Transmembrane protein-related sequences can also possess or interact with domains designated as differentially expressed in neoplastic vs. normal cells "DENN" domains, which are involved in signal transduction. Characteristically, these domains are found in protein components of signaling pathways that utilize rab proteins or mitogen-activated protein (MAP) kinases (<http://pfam.wustl.edu/cgi-bin/getdesc?name=DENN>).

[033] Transmembrane protein-related sequences can also possess or interact with acyl coA binding protein (ACBP) domains, which are protein domains that bind medium- and long-chain acyl-CoA esters with high affinity (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ACBP>). Membrane-related sequences also possess or interact with SPFH domain/band 7 family (Band\_7) domain, which are protein domains that include a transmembrane segment, and regulate cation conductivity ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Band\\_7](http://pfam.wustl.edu/cgi-bin/getdesc?name=Band_7)).

[034] Transmembrane proteins that are differentially expressed on the surface of cancer cells, particularly those that are differentially expressed on the surface of cancer cells but not on the surface of normal tissues, such as heart and lung, are desirable targets for production of antibodies, e.g., diagnostic antibodies or therapeutic antibodies, such as antibodies that mediate ADCC or CDC to effect tumor cell killing.

[035] Transmembrane proteins with extracellular fragments that can be cleaved can be useful as secreted proteins to effect ligand/receptor binding so as to mediate intracellular responses, such as signal transduction. Transmembrane proteins that act as receptors, and possess a ligand binding extracellular portion exposed on a cell surface and an intracellular portion that interacts with other cellular components upon activation can be also be useful as transmembrane proteins to mediate intracellular responses, such as signal transduction.

#### **Kinase-Related Sequences**

[036] A kinase is an enzyme that catalyzes the transfer of phosphate groups from phosphate donors to acceptor substrates. Kinase substrates include, but are not limited to, proteins and lipids. Sequences of the invention that phosphorylate protein substrates are designated "Pkinases." Examples of kinase-related sequences include calcium, calmodulin-dependent protein kinase II, myosin light chain kinase, and phosphatidylinositol kinase.

[037] Kinases and phosphatases are counteracting: kinases add phosphate groups and phosphatases liberate phosphate groups. The counteracting activities of kinases and phosphatases provide cells with a "switch" that can turn on or turn off the function of various proteins. The activity of any protein regulated by phosphorylation depends on the balance, at any given time, between the activities of the kinase(s) that phosphorylate it, and the phosphatase(s) that dephosphorylate it. Phosphorylation plays a important role in intercellular communication during development, homeostasis, and the function of major bodily systems, including the immune system.

[038] In conjunction with phosphatases, kinases control such diverse and essential cellular processes as transcription, cell division, cell cycle progression, differentiation, cytoskeletal function, apoptosis, receptor function, learning and memory, hematopoiesis, fertilization, neural transmission, muscle contraction, non-muscle motor function, glycogen metabolism, and hormone secretion.

[039] Most kinases act within a network of kinases and other signaling effectors, and are modulated by autophosphorylation and phosphorylation by other kinases (Manning et al., 2002). Intracellular signaling involves a multitude of diverse mechanisms that combine to modulate the activity of individual proteins in response to different biological inputs.

[040] Defects in cell signal transduction pathways are responsible for a number of disorders, including the majority of cancers, immune disorders, and many

inflammatory conditions, including, but not limited to, Crohn's disease (Geffen and Man, 2002; Van Den Blink et al., 2002; Lodish 1999). Over-expression and/or structural alteration of kinases, for example, receptor tyrosine kinase family members, is often associated with human cancers. For example, tumor cells are known to use receptor tyrosine kinases in transduction pathways to achieve tumor growth, angiogenesis and metastasis. Therefore, receptor tyrosine kinases represent pivotal targets in cancer therapy. A number of small molecule receptor tyrosine kinase inhibitors have been synthesized, are in clinical trials, are being analyzed in animal models, or have been marketed. Inhibitory mechanisms include ligand-dependent down regulation, e.g., by the adaptor Cbl (Brunelleschi et al., 2002).

[041] Kinase-related sequences can possess or interact with protein kinase (pkinase) domains, which share a conserved catalytic core common in serine/threonine and tyrosine protein kinases (<http://pfam.wustl.edu/cgi-bin/getdesc?name=pkinase>). Kinase-related sequences can also possess or interact with A-kinase anchoring protein 95 (AKAP95) domains, which comprise two zinc fingers, and have been implicated in chromosome condensation (<http://pfam.wustl.edu/cgi-bin/getdesc?name=AKAP95>). Kinase-related sequences can also possess or interact with inositol 1,3,4,-trisphosphate 5/6 kinase (Ins134\_P3\_kin) domains, which mediate the function of inositol 1.3.4-trisphosphate, a branch point in inositol phosphate metabolism ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ins134\\_P3\\_kin](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ins134_P3_kin)).

[042] Kinases, by virtue of their participation in many and varied intracellular activities, are useful as targets of therapeutic intervention such as, for example, in cancer and inflammation. Cells transfected with cDNA encoding a kinase can be used in screening for small molecule agonists or antagonists, for example.

#### **Ligase-Related Sequences**

[043] Ligases are enzymes that join together, or ligate, two molecules. Ligase substrates include nucleic acids and proteins. For example, DNA ligases link two DNA molecules together; they play a role in DNA repair and replication. DNA ligases also are involved in the rearrangement of immunoglobulin gene segments, such as those responsible for the generation of antibody diversity. Examples of protein ligases include ubiquitin protein ligases, which add an ubiquitin molecule to an amino acid residue, typically as part of a peptide or polypeptide. Examples of nucleic acid ligases include DNA ligase I, DNA ligase III alpha, and T4 RNA ligase 2.



[044] Ligases are also involved in cellular regulatory processes. For example, glutamate-cysteine ligase (GCL) is the first and rate-limiting enzyme involved in the biosynthesis of glutathione. Polymorphisms of human GCL account for differences in sensitivity to environmental toxicants and chemotherapeutic agents in human cancer cell lines (Walsh et al., 2001). Also by way of example, glutamate-ammonia ligase, or glutamine synthetase (GS), is expressed at a higher than normal level in human primary liver cancer, and may be involved in hepatocyte transformation (Christa et al., 1994).

[045] Ligase-related sequences can possess or interact with ATP dependent DNA ligase (DNA\_ligase) domains, which can join two DNA fragments by catalyzing the formation of an internucleotide ester bond between a phosphate and a deoxyribose ([http://pfam.wustl.edu/cgi-bin/getdesc?name=DNA\\_ligase](http://pfam.wustl.edu/cgi-bin/getdesc?name=DNA_ligase)). Ligase-related sequences can also possess or interact with glutamate-cysteine ligase (GCS) domains, which catalyze the rate-limiting step in the biosynthesis of glutathione. (<http://pfam.wustl.edu/cgi-bin/getdesc?name=GCS>). Ligase-related sequences can also possess or interact with 2',5' RNA ligase (2\_5\_ligase) domains, which ligate tRNA half molecules containing 2',3'-cyclic phosphate and 5' hydroxyl terminal to products containing a 2'5' phosphodiester linkage ([http://pfam.wustl.edu/cgi-bin/getdesc?name=2\\_5\\_ligase](http://pfam.wustl.edu/cgi-bin/getdesc?name=2_5_ligase)).

[046] Like kinases, ligases are also useful as targets for identification of agonists and antagonists, such as small molecule drugs.

#### **Receptor-Related Sequences (Including Nuclear Hormone and T-Cell Receptors)**

[047] A receptor is a polypeptide that binds to a specific signaling molecule and initiates a cellular response. Receptors can be present on the cell surface or inside the cell. Example of receptor types include G-protein-linked receptors, ion channel-linked receptors, enzyme-linked receptors, T-cell receptors, thyroid hormone receptors, retinoid receptors, nuclear hormone receptors, and the related category of steroid hormone receptors, e.g., cortisol receptors (Alberts et al., 1994).

[048] G-protein-linked receptors transduce extracellular signals into intracellular responses by interacting with guanine nucleotide binding proteins. The same ligand can activate many different G-protein-linked receptors. G-protein-linked receptors mediate cellular responses to a diverse range of signaling molecules, including hormones, neurotransmitters, and local mediators, which are varied in

structure and function, and encompass proteins and small peptides, as well as amino acids and their derivatives, and fatty acids and their derivatives. Many signaling molecules are active at low concentrations, and their receptors often bind with high affinity. Examples of G-protein-linked receptors include, but are not limited to, rhodopsins, olfactory receptors, and  $\beta$ -adrenergic receptors.

[049] Ion channel-linked receptors are involved in synaptic signaling. These receptors regulate ion channels, to which they are linked. Some respond to signals from neurotransmitters, e.g., acetylcholine, serotonin, GABA, and glycine. A common mechanism of action for ion channel-linked receptors is to transiently open or close their respective ion channel, transiently changing the permeability of the membrane in which they reside to a specific ion or ions.

[050] Enzyme-linked receptors can be linked to enzymes or can function as enzymes. Their ligand binding site is commonly on one side of the membrane, e.g., an extracellular domain, and the catalytic site is on the other, e.g., a cytoplasmic domain. Transmembrane tyrosine-specific protein kinase receptors for growth and differentiation factors are enzyme-linked receptors; examples include receptors for epidermal growth factor (EGF), platelet-derived growth factor (PDGF), fibroblast growth factors (FGFs), hepatocyte growth factors (HGF), insulin, insulin like growth factor-1 (IGF-1), nerve growth factor (NGF), vascular endothelial growth factor (VEGF), and macrophage colony stimulating factor (M-CSF).

[051] Nuclear hormone receptors generally function by crossing the plasma membrane of target cells and binding to intracellular protein ligands. Ligand binding activates these receptors in some instances, exposing a DNA binding domain which regulates the transcription of specific genes. Generally, nuclear hormone receptors bind to specific DNA sequences adjacent to or in the vicinity of the genes regulated by their ligand. A host of cell type-specific regulatory proteins can collaborate with the nuclear hormone receptor to influence the transcription of specific genes or sets of genes (Alberts et al., 1994). Examples of nuclear hormone receptors include estrogen-related receptors, such as hERR1, which modulates the estrogen receptor-mediated response of the lactoferrin gene promoter (Yang et al., 1996), and is a transcriptional regulator of the human medium chain acyl coenzyme A dehydrogenase gene (Sladek et al., 1997). Examples of nuclear hormone receptors also include photoreceptor-specific nuclear receptors, such as NR2E3, which are part

of a large family of nuclear receptor transcription factors involved in signaling pathways. NR2E3 plays a role in cone function and human retinal photoreceptor differentiation and degeneration (Milam et al., 2002; Kobayashi et al., 1999).

[052] T-cell receptors are membrane proteins comprised of two disulfide-linked polypeptide chains, each with two immunoglobulin-like domains. They display a similarity to antibodies in that they have a variable amino-terminal region and a constant carboxyl-terminal region which is coded for by variable, joining, and constant region genes (Wei et al., 1997; Alberts et al., 1994). Rearrangement of T-cell receptor genes have been associated with human T-cell leukemias (Fisch et al., 1993).

[053] Receptors are involved in cellular processes that regulate growth and differentiation. Their dysregulation can lead to hyperproliferative conditions, and they are common therapeutic targets. For example, the EGF receptor is aberrantly activated in neoplasia, especially in tumors of epithelial origin. EGF receptor antagonists can successfully treat some of these tumors, either alone or in combination with chemotherapy or ionizing radiation (Kari et al., 2003). The progesterone receptor, an intracellular steroid hormone receptor, plays a role in the development and function of the mammary gland, the uterus, and the ovary. Mutation or aberrant expression of the progesterone receptor, or its regulatory molecules, can affect its normal function and lead to cancer (Gao and Nawaz, 2002).

[054] Receptors are also involved in cellular processes that regulate inflammation and immunity. For example, members of the type 1 interleukin-1 receptor family mediate immune and inflammatory responses, and function in host defense. (O'Neill, 2002). Their activation can lead to the activation of signaling cascades, e.g., pathways involving transcription factors and protein kinases, resulting in an inflammatory response (O'Neill, 2002). Another mechanism by which receptors regulate inflammation and immunity is by their selective expression, at discrete stages of differentiation, by cells involved in the inflammatory response. For example, expression of the triggering receptor expressed on myeloid cells (TREM-1) and the myeloid DAP12-associating lectin (MDL-1) are correlated with myelomonocytic differentiation. These receptors are more highly expressed in differentiated cells, are involved in monocyte activation and the inflammatory response, and are expressed at a lower level in malignant compared to normal cells (Gingras et al., 2002).

[055] Receptor-related sequences can possess or interact with seven transmembrane receptor (7tm\_1) domains, which are protein domains with a structural framework comprising seven transmembrane helices found in receptors, e.g., receptors in the rhodopsin family with a wide range of functions, activated by ligands that vary widely in structure and character ([http://pfam.wustl.edu/cgi-bin/getdesc?name=7tm\\_1](http://pfam.wustl.edu/cgi-bin/getdesc?name=7tm_1)). Receptor-related sequences can also possess or interact with L1 transposable element (transposase\_22) domains, some of which have been characterized to exhibit reverse transcriptase activity, and some of which are capable of retrotransposition. Receptor-related sequences can also possess or interact with a SH2 domain, which is a protein domain of about 100 amino acid residues found in many intracellular signal-transducing proteins, that can regulate intracellular signaling cascades by interacting with phosphotyrosine-containing target peptides in a sequence-specific and phosphorylation-dependent manner (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SH2>). Receptor-related sequences can also possess or interact with LDL receptor domains, e.g., the low-density lipoprotein receptor repeat class B (Ldl\_recept\_b) domain, which comprises a conserved YWTD motif in multiple tandem repeats ([http://pfam.wustl.edu/cgi-bin/getdesc?name=ldl\\_recept\\_b](http://pfam.wustl.edu/cgi-bin/getdesc?name=ldl_recept_b)). Receptor-related sequences can also possess or interact with ribosomal L10 (Ribosomal\_L10e) domains, which are protein domains commonly found in the large ribosomal subunit ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_L10e](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_L10e)).

[056] Receptor-related sequences can possess or interact with zinc finger C4 type domains, which are DNA binding domains of nuclear hormone receptors that share a conserved cysteine-rich region of approximately 65 amino acids and regulate such diverse biological processes as pattern formation, cellular differentiation, and homeostasis (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF00105>). Receptor-related sequences can also possess or interact with a ligand binding domain of nuclear hormone receptors (hormone\_rec), which are helical domains involved in the regulation of eukaryotic gene expression, cellular proliferation, and differentiation in target tissues (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF00104>). Receptor-related sequences can also possess or interact with Mov34 domains, which are regulatory subunits of the proteasome found in some regulators of transcription factors (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF01398>). Receptor-related sequences can also possess or interact with immunoglobulin domains, which are described above.

[057] Receptors, and fragments of receptors can be used as therapeutics. For example, a ligand-binding portion, an effector-binding portion, and a kinase or phosphatase domain or consensus sequence can comprise fragments that can function as agonists or antagonists enhance or reduce, e.g., ligand binding to the natural receptors, or effector function by the natural receptors.

#### **Phosphatase-Related Sequences**

[058] A phosphatase, as indicated above, is an enzyme that catalyses the hydrolysis of esters of phosphoric acid. Its substrates include, but are not limited to, nucleic acids, proteins, and lipids. Together with kinases, phosphatases are active in a broad range of cellular functions, including transcription, cell division, cell-cycle progression, intermediate cellular metabolism, glycogen metabolism, lipogenesis and lipolysis, maintenance of electrochemical gradients, neuronal function, immune responses, intracellular vesicular transport, cytoskeletal function, sperm motility, and skeletal, cardiac, and smooth muscle function (Oliver and Shenolikar, 1998).

[059] Disruption in these functions may lead to disorders. For example, as noted above, phosphatases regulate pathways of cell growth and programmed cell death; disruptions in these pathways can lead to abnormal cell growth, such as that which occurs in cancer. Mutations in serine/threonine protein phosphatase 2A (PP2A), a multifunctional regulator of cell growth and function, are associated with the increased growth of tumor cells (Schonthal, 2001). The tumor suppressor "phosphatase and tensin-homology deleted on chromosome 10" (PTEN) gene encodes PIP<sub>3</sub>, a lipid phosphatase that dephosphorylates phosphatidylinositol, thus countering the action of the oncogenes PI<sub>3</sub>-kinase and Akt, which promote cell survival. PTEN has been identified as a tumor suppressor; it is deleted in multiple types of advanced human cancers.

[060] Also as noted above, phosphatases regulate pathways that control immune function. For example, the CD45 phosphotyrosine phosphatase is one of the most abundant glycoproteins expressed on immune cells, and regulates T-cell signaling and development (Alexander, 2000). In addition, the serine/threonine phosphatase calcineurin plays a central role in lymphocyte activation, among other important and wide-ranging cellular functions (Baksh and Burakoff, 2000). Certain compounds, specifically, cyclosporine and FK-506 (Tacrolimus), have been found to inhibit the phosphatase activity of calcineurin, thereby suppressing the production of IL-2 and other cytokines. In addition, these compounds have recently been found to

block the JNK and p38 signaling pathways triggered by antigen recognition in T-cells. Finally, phosphatase inhibitors have proven to be valuable as immune suppressant drugs, and those in the field believe that modulators of phosphatase activity promise to be important immunoregulatory compounds (Allison, 2000).

[061] Phosphatase-related sequences can possess or interact with protein phosphatase 2C (PP2C) domains, which display  $Mn^{++}$  or  $Mg^{++}$  dependent protein serine/threonine phosphatase activity (<http://pfam.wustl.edu/cgi-bin/getdesc?name=PP2C>). Phosphatase-related sequences can also possess or interact with protein-tyrosine phosphatase (Y\_phosphatase) domains, which catalyze the removal of a phosphate group attached to a tyrosine residue ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Y\\_phosphatase](http://pfam.wustl.edu/cgi-bin/getdesc?name=Y_phosphatase)). Phosphatase-related sequences can also possess or interact with protein phosphatase inhibitor 1/DARPP-32 (DARPP-32) domains, which inhibit protein phosphatases, and play a role in regulating neurotransmitter pathways, receptors, and ion channels (<http://pfam.wustl.edu/cgi-bin/getdesc?name=DARPP-32>).

[062] Like kinases, phosphatases can be used as targets for therapeutic intervention, in cell-free or cell-based assays, for example, in screening for drugs, including small molecule drugs.

#### **Protease-Related Sequences**

[063] Proteases, also known as endopeptidases, are enzymes that cleave polypeptide chains by hydrolyzing peptide bonds at positions within the amino acid chain. Different proteases recognize different polypeptide sequences. Endopeptidase substrate specificities vary from broad to narrow; for example, subtilisins are relatively non-specific, and can cleave polypeptide chains with a wide variety of amino acid sequences, whereas thrombin is more specific and can only cleave polypeptide chains with an arginine residue on the carboxyl side of the susceptible peptide bond and glycine on the amino side. Additional examples of protease-related sequences include collagenases, trypsin, and damage-induced neuronal endopeptidase (Kiryu-Seo et al., 2000).

[064] Proteases mediate the continuous remodeling of living tissues. For example, the extracellular matrix, a tissue skeleton that mediates communication among cells, and influences the structure and function of associated tissues and organs, is continuously remodeled. A strictly controlled balance is maintained between breakdown of the extracellular matrix by proteases and reconstruction of the

extracellular matrix. This continued matrix remodeling is a dynamic process that shapes the structure and function of tissues and organs (Wojtowicz-Praga, 1999).

[065] Defects in protease function are responsible for a number of disorders, including cancer and other hyperproliferative disorders. Proteases are involved in the pathogenesis of such disorders both by virtue of their involvement in programmed cell death and tumor invasion and metastasis (Los et al., 2003; Stetler-Stevenson et al., 1993). Detection of the presence or characteristics of proteases can be used to screen for and diagnose prostate cancer (Karanazanashvili and Abrahamsson, 2003). Proteases are also involved in the pathogenesis of inflammatory and arthritic diseases, such as pancreatitis, osteoarthritis, and rheumatoid arthritis (Pfitzer and Whitcomb, 2001; Martel-Pelletier et al., 2001; Lerch and Gorelick, 2000).

[066] Protease-related sequences possess or interact with a variety of different protease domains, including domains belonging to the cysteine protease family, the serine protease family, and the metalloproteinase family ([http://pfam.wustl.edu/cgi-bin/textsearch?terms=endopeptidase&search\\_what=all&sections=DE&sections=CC&size=10](http://pfam.wustl.edu/cgi-bin/textsearch?terms=endopeptidase&search_what=all&sections=DE&sections=CC&size=10)).

#### **Phosphodiesterase-Related Sequences**

[067] Phosphodiesterases are enzymes that cleave phosphodiester bonds, i.e., bonds formed by two hydroxyl groups in an ester linkage to the same phosphate group, such as those between adjacent RNA or DNA nucleotides. Phosphodiesterases are found in both soluble and membrane-associated forms. Most phosphodiesterases act within a network of signal transduction molecules and other signaling effectors, and are modulated by components of these pathways. Phosphodiesterases regulate the metabolism and synthesis of cyclic nucleotides in signal-transduction pathways. They hydrolyze cAMP and cGMP, molecules that play an important and widespread role in signal transduction. Phosphodiesterases also repair damage to nucleic acids. Some phosphodiesterases are regulated primarily by calcium and calmodulin, others are regulated primarily by cGMP. They differ in their sensitivity to individual inhibitors, but all share a homologous catalytic region (Siegel, et al., 1999).

[068] Examples of phosphodiesterases include nucleotide pyrophosphatases (NPP) and plasma membrane glycoprotein PC-1, which are present in elevated levels in the fibroblasts of patients with Lowe's syndrome (Funakoshi et

al., 1992). Another example of a phosphodiesterase is myomegalin-like protein, which is expressed at high levels in the nucleus and cytoplasm of heart and skeletal muscle (Soejima et al., 2001). Phosphodiesterases have demonstrated promise in cancer chemotherapy, analgesia, the treatment of Parkinson's disease, and the treatment of learning and memory disorders (Weishaar, et al., 1985).

[069] Phosphodiesterase-related sequences can possess or interact with type I phosphodiesterase/nucleotide pyrophosphatase (phosphodiester) domains, which catalyze the cleavage of phosphodiester and phosphosulfate bonds (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF01663>). Phosphodiesterase-related sequences can also possess or interact with 3'5'-cyclic nucleotide phosphodiesterase (PDEase) domains, which are involved in signal transduction (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF00233>).

[070] Phosphodiesterases (PDEs) are also useful as targets for therapeutic intervention, for example, for identification of agonists or antagonists, such as in the screening of small molecule inhibitors. A well known PDE-5 inhibitor, sildenafil citrate (Viagra®) is used for treatment of erectile dysfunction (Brock, 2000). The mechanism of action involves inhibition of PDE-5 enzyme and resulting increase in cyclic guanosine monophosphate (cGMP) and smooth muscle relaxation in the penis (Rosen and McKenna, 2002). Such inhibitors may also find use for treatment of severe pulmonary arterial hypertension. (Ghofrani et al., 2003).

#### **Kinesin-Related Sequences**

[071] Cells transport proteins and organelles in an orderly and regulated manner along cytoskeletal filaments. Molecular motor proteins, such as kinesins, can carry such cargo along the cytoskeletal filaments to specific destinations, in a highly regulated manner. Exemplary membrane-bound cargoes include mitochondria, lysosomes, endoplasmic reticulum, and axonal vesicles (Vale, 2003). Kinesins also transport nonmembranous cargo, such as mRNAs, tubulin monomers, and intermediate filaments (Vale, 2003).

[072] Kinesins, e.g., KIF11, function in the cell division process (Miki et al., 2001). In the nucleus, kinesins are necessary to establish spindle bipolarity, position chromosomes on metaphase plates, and maintain forces in the spindle. Several members of the kinesin family are associated with the chromosomes, and are likely to perform a role in mitotic chromosome movement (Miki et al., 2001). For example, the C-terminal kinesin KIFC1 is involved in the processes of meiosis,



mitosis, and karyogamy (Miki et al., 2001). The kinesin GAKIN binds to the human analog of the *Drosophila* Discs Large tumor suppressor protein (hDlg), a membrane associated guanylate kinase (Hanada, 2000). GAKIN undergoes translocation in T-lymphocytes upon their cellular activation (Hanada, 2000). The GAKIN/hDlg complex is also hypothesized to play a role in cell division (Hanada, 2000). Thus, the kinesin GAKIN plays a role in cell proliferation and T-cell mediated immune function.

[073] Kinesin-mediated intracellular transport is also implicated in as a mechanism of tumorigenesis. For example, kinesin transports the tumor suppressor adenomatous polyposis colon protein (APC) (Jimbo et al., 2002). The APC gene is mutated in both sporadic and familial colorectal tumors. The APC protein interacts with the microtubule plus-end-directed kinesin proteins KIF3A and KIF3B through an association with the kinesin superfamily-associated protein 3 (KAP3). Normally, the APC tumor suppressor is transported to its correct intracellular location at the tips of membrane protrusions. Mutant APCs derived from cancer cells, however, are unable to undergo kinesin-mediated transport, and do not accumulate with normal efficiency in clusters in the membrane protrusions, and thereby can not function efficiently as tumor suppressors.

[074] In view of the connection to cancer, investigators have sought small molecules to inhibit specific molecular motors in cells, such as the mitotic kinesin Eg5/Ksp (Mayer, 1999). In addition, others have found small molecule inhibitors of Eg5/Kap with low nanomolar affinity have anti-tumor activity, and one such agent has entered clinical phase I trials (Vale, 2003).

[075] In another arena, it has been proposed that impairing motor-driven delivery of MHC peptide complexes to the surface of dendritic cells could provide immunomodulation. Additionally, inhibiting the cell surface delivery of cytotoxic granules in T cells could help provide immunosuppressive therapy (Vale, 2003).

[076] Kinesin-related sequences can possess or interact with kinesin motor (kinesin) domains, which hydrolyze ATP and bind to microtubules to produce a motor-active force that transports intracellular vesicles and organelles (<http://pfam.wustl.edu/cgi-bin/getdesc?name=kinesin>). Kinesin-related sequences can also possess or interact with kinesin-associated protein (KAP) domains, which are non-motive domains that form a complex with kinesin (<http://pfam.wustl.edu/cgi->

bin/getdesc?name=KAP). Kinesin-related sequences can also possess or interact with MyTH4 domains, which are present in the tail of the motor ATPase proteins kinesin and myosin (<http://pfam.wustl.edu/cgi-bin/getdesc?name=MyTH4>).

[077] Kinesins, like kinases, are useful as targets for therapeutic intervention, for example, in screening for small molecule inhibitors for the treatment of cancer.

### **Immunoglobulin-Related Sequences**

[078] An immunoglobulin is an antibody molecule, and is typically composed of heavy and light chains, each of which have constant regions that display similarity with other immunoglobulin molecules and variable regions that convey specificity to particular antigens. Most immunoglobulins can be assigned to classes, e.g., IgG, IgM, IgA, IgE, and IgD, based on antigenic determinants in the heavy chain constant region; each class plays a different role in the immune response.

[079] Immunoglobulins are characterized by a structural motif, the immunoglobulin (Ig) domain, which is approximately one hundred amino acids long, is involved in protein-protein and protein-ligand interactions, and includes a conserved intradomain disulfide bond (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ig>). It is one of the most common domains found among all known proteins, and is present in hundreds of proteins with diverse functions. Proteins with the Ig domain comprise the immunoglobulin superfamily; members include antibodies, T-cell receptors, major histocompatibility proteins, the CD4, CD8, and CD28 co-receptors, most of the invariant polypeptide chains associated with B and T cell receptors, leukocyte Fc receptors, the giant muscle kinase titin, and receptor tyrosine kinases (Janeway et al., 2001; Alberts, et al., 1994).

[080] Polypeptides with immunoglobulin-like domains can be markers for specific types of tissues and tumors. For example, a 43-kDa protein membrane antigen with two immunoglobulin-like domains in its extracellular region is expressed in normal human colonic and small bowel epithelium and > 95% of human colon cancers, but absent from most other human tissues and tumor types (Heath et al., 1997).

[081] Polypeptides with immunoglobulin-like domains are also involved in inflammation. For example, myelin oligodendrocyte glycoprotein, a myelin-specific protein found in the central nervous system, specifically binds to and activates complement, an effector of the immune system, via its extracellular immunoglobulin-

like domain. By virtue of providing the means for an interaction between myelin and the complement component of the immune response, myelin oligodendrocyte glycoprotein is a modulator of central nervous system inflammation and has been predicted by those in the field to be relevant to the pathogenesis of demyelinating diseases such as multiple sclerosis (Johns and Barnard, 1997).

[082] Immunoglobulin-related sequences can also possess or interact with leucine-rich repeat domains, which are involved in protein-protein interactions, and are used in molecular recognition processes as diverse as signal transduction, cell adhesion, cell development, DNA repair and RNA processing (<http://pfam.wustl.edu/cgi-bin/getdesc?name=LRRNT>). Immunoglobulin-related sequences can also possess or interact with fibronectin type III repeat (fn3) domains (<http://pfam.wustl.edu/cgi-bin/getdesc?name=fn3>), which contain binding sites for DNA and heparin. Immunoglobulin-related sequences can also possess or interact with WASp Homology domain 1 (WH1), which can bind the metabotropic glutamate receptors mGluR1alpha and mGluR5 (<http://pfam.wustl.edu/cgi-bin/getdesc?name=WH1>).

#### **Glycosylphosphatidylinositol Anchor-Related Sequences**

[083] Glycosylphosphatidylinositol (GPI) anchor proteins are synthesized as single membrane proteins; the transmembrane segment is cleaved away in the endoplasmic reticulum, where a GPI membrane anchor is added. The resulting protein is bound to the non-cytoplasmic, i.e., either extracellular or luminal, side of the membrane by the GPI anchor. GPI anchor proteins can be dissociated from the membrane by phosphatidylinositol-inositol-specific phospholipase C (Alberts et al., 1994). Examples of GPI-anchor proteins include prefoldin, a chaperone that delivers unfolded proteins to cytosolic chaperonin (Vainberg et al., 1998), and carboxypeptidase M, which is associated with the differentiation of monocytes to macrophages (Rehli et al., 1995).

[084] GPI anchor protein-related sequences can possess or interact with KE2 domains, which may contain a DNA binding leucine zipper motif (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF01920>). GPI anchor protein-related sequences can also possess or interact with zinc carboxypeptidase (Zn\_carboPept) domains, which include carboxypeptidase H regulatory domains and carboxypeptidase A digestive domains (<http://www.sanger.ac.uk/cgi-bin/Pfam/getacc?PF00246>).

## Other Polypeptide-Related Sequences

### Activator-Related Sequences

[085] An activator is a molecule or collection of molecules that positively modulates the activity of a regulatory protein, or that binds to DNA and regulates one or more genes by increasing the rate of transcription. Regulatory protein activators contribute to an increase in protein activity. Transcriptional activators provide a positive control over gene transcription; for example, they can sense the internal condition of the cell and bind to a sequence of DNA near a target promoter, resulting in the transcription of an appropriate gene. Examples of activator-related sequences include template-activating factors, bacterial catabolite activators, and the coenzyme thiamine pyrophosphatase. Activator-related sequences, e.g., factors that influence viral replication and transcription, can be encoded by oncogenes (Nagata et al., 1995).

[086] Activator-related sequences can possess or interact with SH2 domains, which are protein domains of about 100 amino acid residues found in many signal-transducing proteins. SH2 domains can regulate signaling cascades, e.g., by interacting with phosphotyrosine-containing target peptides in a sequence-specific and phosphorylation-dependent manner (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SH2>). Activator-related sequences also possess or interact with nucleosome assembly protein (NAP) domains, which regulate gene expression, and are accessible to histones (<http://pfam.wustl.edu/cgi-bin/getdesc?name=NAP>).

### Adaptor-Related Sequences

[087] Adaptors are proteins involved in the process of capturing specific cargo molecules into membrane-bound vesicles for transport through the cell. Different adaptors recognize different receptors for cargo molecules, and also recognize different vesicle coat proteins, accounting, in part, for the specificity of the content of intracellular vesicles bound to specific destinations within the cell (Kirsch et al., 1999). Examples of adaptor-related sequences include adaptins, clathrins, adaptor-related protein complex subunits, and Cas ligand with multiple Src homology 3 domains (CMS) adaptors.

[088] Adaptor-related sequences can possess or interact with src homology 3 (SH3) domains, which are small protein modules of approximately 50 amino acid residues found in a variety of intracellular or membrane-associated proteins. SH3 domains are often indicative of a protein involved in signal

transduction events related to cytoskeletal organization. (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SH3>). Adaptor-related sequences also possess or interact with the adaptin N-terminal (Adaptin\_N) protein domain, which is found in the N terminal region of various adaptor protein complexes. The N-terminal region of adaptor proteins is relatively constant in comparison to the C-terminal ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Adaptin\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=Adaptin_N)).

#### **Adhesion Molecule-Related Sequences**

[089] Adhesion molecules are molecules that mediate the adhesion of cells with other cells, and with the extracellular matrix. Examples of adhesion molecules include members of the immunoglobulin superfamily, integrins, cadherins, selectins, and transmembrane proteoglycans. The adhesion molecule carcinoembryonic antigen (CEA) is present nearly exclusively on cancer cells, and is expressed on the cell surface of approximately 80% of all solid cancerous tumors (Berinstein et al., 2002).

[090] Adhesion molecule-related sequences can possess or interact with the immunoglobulin (ig) domain, which are described above. Adhesion molecule-related sequences can also possess or interact with integrin alpha cytoplasmic region (integrin\_A) domains, which comprise the short, intracellular region of the integrin alpha chain [http://pfam.wustl.edu/cgi-bin/getdesc?name=integrin\\_A](http://pfam.wustl.edu/cgi-bin/getdesc?name=integrin_A).

#### **Antigen-Related Sequences**

[091] An antigen is a molecule that provokes an immune response; they include both foreign antigens and autoantigens. Antigens can be expressed in a tissue-specific manner and their expression can be developmentally regulated. For example, the heat stable antigen HSA is expressed in both a tissue-specific manner, i.e., it is restricted to hematopoietic cells, and a developmentally-regulated manner, i.e., it is more highly expressed in immature precursor cells than in terminally differentiated cells (Wenger et al., 1993). Antigens can be expressed on the cell surface or inside the cell, e.g., in the nucleus or on intermediate filaments. Antigen-related sequences include sequences related to tumor antigens, which are expressed exclusively in tumor cells, or in greater amounts in tumor cells than in normal cells. Tumor antigens can be transmembrane proteins, with one or more transmembrane domains (Li et al., 1996; Linnenbach, et al., 1993).

[092] Autoantigens, which are components of the body that provoke an immune response, are involved in the pathogenesis of autoimmune disease.

Autoantigens can be either selectively or ubiquitously expressed among cell and tissue types. They can be localized to any region of the cell, including the nucleus, nucleolus, nuclear envelope, and intermediate filaments (Racevskis et al., 1996). For example, pancreatic islet cell antigens are involved in the autoimmune pathogenesis of diabetes, and thyroid antigens are involved in autoimmune thyroid disease.

[093] Antigen-related sequences can possess or interact with the ICAp69 domain, which is characterized by a 69 kDa pancreatic islet cell autoantigen present in autoimmune (insulin-dependent) diabetes mellitus (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ICA69>). Antigen-related sequences can also possess or interact with the Ku70/Ku80 C-terminal arm (Ku\_C) or Ku70/Ku80 N-terminal alpha/beta (Ku\_N) domains, which belong to the Ku family of peptides ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ku\\_C](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ku_C); [http://pfam.wustl.edu/cgi-bin/getdesc?name=Ku\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ku_N)). Ku, an antigen associated with autoimmune disease, normally functions to bind DNA double-strand breaks and facilitate DNA repair, but induces autoimmunity under pathological conditions. Antigen-related sequences can also possess or interact with the bZIP transcription factor (bZIP) domain, which comprises a basic region and a leucine zipper region (<http://pfam.wustl.edu/cgi-bin/getdesc?name=bZIP>). Antigen-related sequences can possess or interact with YT521-B-like (YTH) domains, which comprise YT521-B, a tyrosine-phosphorylated nuclear protein domain that modulates alternative RNA splice site selection, and interacts with other nuclear proteins, e.g., scaffold attachment factor B, and Sam68, a 68-kDa substrate associated with Src during mitosis (<http://pfam.wustl.edu/cgi-bin/getdesc?name=YTH>).

#### ATPase-Related Sequences

[094] ATPases are enzymes that use the energy of ATP hydrolysis to move ions or small molecules across a membrane against a chemical concentration gradient or electrical potential. For example, ATPases can maintain low intracellular calcium and sodium ion concentrations, and generate a low pH inside lysosomes, plant-cell vacuoles, and the lumen of the stomach. Vacuolar ATPases are ATP-dependent proton pumps that create pH gradients by transporting protons across membranes, while coupling the energy produced in the conversion of ATP to ADP with proton transport (Forgac, 1999). They can acidify or alkalize cells, organelles, and extracellular compartments, and create voltage gradients that drive the secretion or absorption of ions and fluids (Wieczorek et al. 1999). Examples of ATPase-related

sequences include proton transporters, glucose transporters, multidrug resistance factors, calcium ATPases, and porins.

[095] ATPase-related sequences can possess or interact with ATP synthase F<sub>1</sub>/14-kDa subunit (ATP-synt-F) domains, which correspond to a 14-kDa subunit in the peripheral catalytic part of vacuolar ATPases ([http://pfam.wustl.edu/cgi-bin/getdesc?name=ATP-synt\\_F](http://pfam.wustl.edu/cgi-bin/getdesc?name=ATP-synt_F)). ATPase-related sequences can also possess or interact with vacuolar (H<sup>+</sup>)-ATPase C, D, G, and H subunit (V-ATPase) domains, which are membrane-attached sequences that generate an acidic environment ([http://pfam.wustl.edu/cgi-bin/getdesc?name=V-ATPase\\_G](http://pfam.wustl.edu/cgi-bin/getdesc?name=V-ATPase_G)).

#### ATP-Related Sequences

[096] Adenosine triphosphate (ATP) is a nucleotide comprising an adenine, a ribose, and a triphosphate unit. The triphosphate unit contains two phosphoanhydride bonds that confer an energy-rich property to ATP. The free energy liberated in the hydrolysis of one or both of these bonds can drive reactions that require an input of free energy. A wide range of physiological and pathological processes are driven by the energy of ATP, including cellular movement, the synthesis of biomolecules from precursors, muscle contraction, ciliary and flagellar function, intermediary metabolism, glycolysis, fatty acid oxidation, oxidative phosphorylation, and membrane transport (Ku et al., 1990). Examples of ATP-related sequences include ATPases, ATP synthases, ATP carrier proteins, and myosin.

[097] ATP-related sequences can possess or interact with ATP-synthase subunit C protein domains (ATP-synt\_C), which are protein domains that consist of two long terminal hydrophobic regions, and are implicated in the proton-conducting activity of ATPases ([http://pfam.wustl.edu/cgi-bin/getdesc?name=ATP-synt\\_C](http://pfam.wustl.edu/cgi-bin/getdesc?name=ATP-synt_C)). ATP-related sequences can also possess or interact with mitochondrial carrier protein (mito\_carr) domains, which are involved in energy transfer across the inner mitochondrial membrane ([http://pfam.wustl.edu/cgi-bin/getdesc?name=mito\\_carr](http://pfam.wustl.edu/cgi-bin/getdesc?name=mito_carr)).

#### Binding Protein-Related Sequences

[098] A binding protein is a protein that binds to another molecule with specificity. Binding proteins can be involved in building macromolecular structures, e.g., in cytoskeletal assembly or scaffolding (Machesky et al., 1997). Proteins often exist in the cell in complexes with other proteins, nucleic acids, lipids, and/or small molecules. For example, steroid receptors, e.g., the progesterone, estrogen, androgen,

and glucocorticoid receptors, bind to heat-shock proteins and FKBP52, a calcium-regulated immunosuppressant, to form functional complexes (Peattie et al., 1992; Sanchez et al., 1990). DNA binding proteins and general transcription factors bind to the TATA box, a consensus sequence in a gene's promoter region that specifies the position of transcription initiation, forming a functional transcription complex (Chalut et al., 1995). Proteins can interact with multiple molecules simultaneously. For example, Nedd4, an ubiquitin-protein ligase, can interact with multiple proteins and lipids through its lipid binding domain and multiple protein binding domains (Jolliffe et al., 2000).

[099] Proteins utilize a large number of motifs to bind other molecules. Binding protein-related sequences can possess or interact with the cold-shock DNA-binding (CSD) domain, a conserved domain of about 70 amino acids that helps the cell survive in temperatures below optimum growth temperature by inducing the synthesis of proteins that negatively regulate transcription, translation, and recombination, resulting in suppressed cell proliferation (<http://pfam.wustl.edu/cgi-bin/getdesc?name=CSD>). Proteins induced by exposure to cold include DNA-binding proteins, and cold inducible RNA binding proteins, which have RNA binding domains at or near their N-termini (Nishiyama et al., 1997). For example, contrin, a testis-specific DNA/RNA binding protein with a cold shock domain also has a large number of phosphorylation sites, each of which can mediate intermolecular interactions (Tekur et al., 1999). Contrin is involved in transcription of testis-specific genes; its inactivation could provide a reversible male contraceptive.

[0100] Binding protein-related sequences can possess or interact with the ARID/BRIGHT DNA binding (ARID) domain, which is an approximately 100 amino acid sequence involved in a wide range of DNA interactions, including, but not limited to, interaction with AT-rich regions (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ARID>). ARID-encoding genes are involved in a variety of biological processes, including regulation of cell growth, development, cell lineage gene regulation, cell cycle control, and tissue-specific gene expression.

[0101] Binding protein-related sequences can also possess or interact with nucleosomal binding domains to facilitate binding within the nucleosome, a nuclear structure comprised of chromosomal DNA and proteins. For example, the HMG14 and HMG17 (HMG14\_17) domain is present in some nucleosome proteins, most commonly, in proteins HMG14 and HMG17, members of a family designated as high



mobility group proteins, which form components of chromatin, and bind to nucleosomal DNA, regulating the interaction of the DNA with histone proteins ([http://pfam.wustl.edu/cgi-bin/getdesc?name=HMG14\\_17](http://pfam.wustl.edu/cgi-bin/getdesc?name=HMG14_17)).

[0102] Binding protein-related sequences can also possess or interact with conserved motifs that recognize RNA, and allow the protein to bind RNA ([http://pfam.wustl.edu/cgi-bin/textsearch?terms=rna+binding&search\\_what=all&sections=DE&sections=CC&size=100](http://pfam.wustl.edu/cgi-bin/textsearch?terms=rna+binding&search_what=all&sections=DE&sections=CC&size=100)). These motifs include the RNA recognition (rrm) domain, also known as a RRM, RBD, or RNP domain (<http://pfam.wustl.edu/cgi-bin/getdesc?name=rrm>). Numerous RNA binding proteins possess the rrm domain, including heterogeneous nuclear ribonucleoproteins (hnRNP) proteins, which are implicated in the regulation of alternative splicing, and LA proteins, which are among the main autoantigens in systemic lupus erythematosus (SLE).

[0103] Binding protein-related sequences can also possess or interact with conserved motifs that mediate their binding to ions, e.g., calcium. Calcium-binding proteins such as calmodulin, the calcineurins, and their homologues and related proteins are widely used to regulate cellular processes ([http://pfam.wustl.edu/cgi-bin/textsearch?terms=calcium+binding&search\\_what=all&sections=DE&sections=CC&size=100](http://pfam.wustl.edu/cgi-bin/textsearch?terms=calcium+binding&search_what=all&sections=DE&sections=CC&size=100)). Ion-binding proteins include phosphoproteins that bind to other molecules in an manner dependent on their phosphorylation state, and can regulate many types of molecules and processes, including those that utilize complex signaling cascades (Pang et al., 2001; Pang et al., 2002; Lin et al., 1999). Ion-binding protein-related sequences can possess or interact with the EF hand (efhand) domain, a calcium-binding domain that comprises a loop of twelve amino acids that coordinates a calcium ion in a pentagonal bipyramidal configuration and is flanked on both sides by a twelve amino acid alpha-helical domain (<http://pfam.wustl.edu/cgi-bin/getdesc?name=efhand>).

### Breakpoint-Related Sequences

[0104] A breakpoint is the location on a chromosome where a gene is disrupted, and one segment of the gene is severed from the other. Chromosomal breaks that disrupt coding or regulatory sequences can result in gene mutation. Chromosomal breaks can also serve as molecular landmarks, e.g., a break can be detected on Southern blots as the loss of an expected band and the appearance of two novel bands. Examples of breakpoint-related sequences include the sequences that generate the Philadelphia chromosome translocation, the sequences that generate the

chromosome translocation (t(1;7)(q42;p15)), which is implicated in Wilms' tumor, and the sequences that generate the chromosomal translocation t(18;21)(q22.1q21.3), which is implicated in Down syndrome.

[0105] Breakpoints commonly occur in discrete regions of the chromosome. Breakage at these regions can lead to a recognized disease phenotype. One way of generating such a phenotype is by chromosomal translocation, i.e., chromosomes mutate by exchanging parts. When a segment from one chromosome is exchanged with a segment from another nonhomologous chromosome, two mutated chromosomes are simultaneously generated (Griffiths, et al., 1999). The Philadelphia chromosome, a mutation sometimes associated with chronic myelogenous leukemia (CML), is an example. It results from the translocation of a discrete segment of chromosome 22 into a discrete region of chromosome 9. Patients with the Philadelphia chromosome mutation generally have a better prognosis than CML patients with other characteristics.

[0106] Acquired clonal chromosomal abnormalities are found in the malignant cells of most patients with leukemia, lymphoma, and solid tumors. Some of these abnormalities are the result of consistent chromosomal rearrangements. For example, in a preponderant number of chronic myelogenous leukemia cases, breakpoints at chromosome band 22q11 occur within a breakpoint cluster region of 5-6 kb (Weinstein et al., 1988).

[0107] Chromosome rearrangements affecting band 3q21 are associated with a particularly poor prognosis in myeloid leukemia or myelodysplasia. These breakpoints cluster in a breakpoint cluster region of approximately 30 kb, located centromeric and downstream of the ribophorin I (RPN-I) gene (Weiser, 2002). The apoptotic gene *bcl-2*, was isolated as a breakpoint rearrangement in human follicular lymphomas and was shown to act as an oncogene that promoted cell survival rather than cell proliferation.

[0108] Some proteins can act as leukemia or lymphoma-specific antigens for major histocompatibility complex-restricted T cell cytotoxicity. These include the breakpoint cluster region (*bcr*)-*abl*, and other fusion oncoproteins. Genetically engineered chimeric and humanized antibodies have demonstrated activity against overt lymphomas and leukemias. Radioimmunotherapy has produced significant therapeutic responses with minimal radiation exposure to normal tissues (Juric et al., 2000).

[0109] Breakpoint-related sequences can possess or interact with RhoGAP domains, also known as the breakpoint cluster region-homology domain, and mediates signal transduction by small G proteins (<http://pfam.wustl.edu/cgi-bin/getdesc?name=RhoGAP>). Breakpoint-related sequences can also possess or interact with RhoGEF domains, which comprise approximately 200 amino acid residues that encode a guanine nucleotide exchange factor (<http://pfam.wustl.edu/cgi-bin/getdesc?name=RhoGEF>). Breakpoint-related sequences can also possess or interact with Plectin/S10 (S10\_pectin) domains, which are found at the N-terminus of some isoforms of plectin and ribosomal S10 protein ([http://pfam.wustl.edu/cgi-bin/getdesc?name=S10\\_pectin](http://pfam.wustl.edu/cgi-bin/getdesc?name=S10_pectin)).

#### **Carrier or Transport-Related Sequences**

[0110] A membrane transport protein is an integral transmembrane protein that aids one or more molecules across a cell membrane. Most, if not all, types of molecules are transported across membranes, including proteins, ions, and fatty acids (Schaffer and Lodish, 1994). Even molecules such as water and urea, which can diffuse across pure phospholipid bilayers, are frequently accelerated by transport proteins. Transporters clear cells of toxins, and confer drug resistance on tumor lines (Ramalho-Santos et al., 2002). The rate of transport varies considerably among membrane transport proteins. Membrane transport proteins function in the plasma membrane and in intracellular organellar membranes, including the nuclear, mitochondrial, lysosomal, and vesicular membranes. For example, transportin, also known as karyopherin beta2, imports nuclear mRNA binding proteins from the cytoplasm across the nuclear membrane, into the nucleus (Bonifaci et al., 1997).

[0111] Membrane transport proteins can have either a broad or a narrow range of specificity for the transported substance. In mammalian cells, nucleoside transport across membranes is mediated by broad specificity transporters. Nucleoside transport plays a role in such diverse cellular functions as nucleotide synthesis, neurotransmission, and platelet aggregation. Nucleoside transporters carry chemotherapeutic nucleosides, and are a target of interest in chemotherapeutic and cardiac drug design (Griffiths et al., 1997; Ku et al., 1990).

[0112] Carriers are another class of membrane transport proteins; they bind to a solute and transport it across the membrane by undergoing a series of conformational changes. In contrast to channel proteins, transporters bind only one, or a few, substrate molecules at a time; after binding substrate molecules, they

undergo a conformational change such that the bound substrate molecules, and only those molecules, are transported across the membrane. Carriers transport a wide variety of molecules, including fatty acids across the plasma membrane (Schaffer and Lodish, 1994); purines, pyrimidines, and components of nucleosides across the nuclear membrane, and adenine nucleotides across the inner mitochondrial membrane (Battini et al., 1997).

[0113] Membrane transport-related sequences can possess or interact with vacuolar ( $H^+$ -ATPase C, D, G, and H subunit (V-ATPase) domains, which are membrane-attached sequences that generate an acidic environment ([http://pfam.wustl.edu/cgi-bin/getdesc?name=V-ATPase\\_C](http://pfam.wustl.edu/cgi-bin/getdesc?name=V-ATPase_C)). Membrane transport-related sequences can also possess or interact with nucleoside transporter (nucleoside\_tran) domains, which are found in proteins that transport nucleosides across the plasma membrane, and are employed to synthesize nucleotides via the salvage pathways in cells that lack their own de novo synthesis pathways ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Nucleoside\\_tran](http://pfam.wustl.edu/cgi-bin/getdesc?name=Nucleoside_tran)). Membrane transport-related sequences can also possess or interact with ATP synthase F/14-kDa subunit (ATP-synt-F) domains, which correspond to a 14-kDa subunit in the peripheral catalytic part of vacuolar ATPases ([http://pfam.wustl.edu/cgi-bin/getdesc?name=ATP-synt\\_F](http://pfam.wustl.edu/cgi-bin/getdesc?name=ATP-synt_F)). Membrane transport-related sequences can also possess or interact with mitochondrial carrier protein (mito\_carr) domains, which are involved in energy transfer across the inner mitochondrial membrane ([http://pfam.wustl.edu/cgi-bin/getdesc?name=mito\\_carr](http://pfam.wustl.edu/cgi-bin/getdesc?name=mito_carr)). Membrane transport-related sequences can also possess or interact with an AMP-binding enzyme (AMP-binding) domain, which is a domain rich in serine, threonine, and glycine, and is characterized by a conserved proline-lysine-glycine triplet sequence (<http://pfam.wustl.edu/cgi-bin/getdesc?name=AMP-binding>).

[0114] Membrane transport proteins, such as those expressed in cancer cells, are useful as targets for therapeutic intervention, for example, in the screening for small molecule inhibitors. Inhibition of membrane transport, as indicated above, may make cancer cells more susceptible to chemotherapy, for example.

#### **Channel-Related Sequences**

[0115] Channel proteins transport water or specific types of ions down their concentration or electrical potential gradients. They form a protein-lined passageway across the membrane through which multiple water molecules or ions

move at a very rapid rate, e.g., up to  $10^8$  per second. The plasma membrane, for example, contains potassium-specific channel proteins that generate the cell's resting electric potential across the plasma membrane. Examples of channel-related sequences include the sodium hydrogen exchanger, sodium potassium ATPase, and the cystic fibrosis transmembrane regulator.

[0116] Members of this subset of membrane transport proteins have wide-ranging functions in both normal physiology and in pathology. For example, the transport system that mediates the transmembrane exchange of sodium for hydrogen across the plasma membrane plays a physiological role in the regulation of intracellular pH, the control of cell growth and proliferation, stimulus-response coupling, metabolic responses to hormones, the regulation of cell volume, and the transepithelial absorption and secretion of several ions. The sodium-hydrogen exchanger also plays a role in cancer and in tissue and organ hypertrophy (Mahnensmith and Aronson, 1985).

[0117] Channel-related sequences can possess or interact with sodium/hydrogen exchanger (Na\_H\_Exchanger) domains, which exchange sodium for hydrogen across a membrane in an electroneutral manner ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Na\\_H\\_Exchanger](http://pfam.wustl.edu/cgi-bin/getdesc?name=Na_H_Exchanger)). Channel-related sequences can also possess or interact with neurotransmitter-gated ion-channel ligand binding (Neur\_chan\_LBD) domains, which form the extracellular domains of some ion channels ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Neur\\_chan\\_LBD](http://pfam.wustl.edu/cgi-bin/getdesc?name=Neur_chan_LBD)). Channel-related sequences can also possess or interact with UBX domains, which are present in ubiquitin-regulatory proteins (<http://pfam.wustl.edu/cgi-bin/getdesc?name=UBX>).

#### **Checkpoint-Related Sequences**

[0118] The cell division cycle is the fundamental means by which living things are propagated. Fundamental to successful propagation is the faithful replication of DNA; a cell cycle control system exists to coordinate the cycle as a whole. The control system is regulated by brakes that can stop the cycle at specific checkpoints. Thus, the checkpoints arrest the cycle upon the occurrence of undesirable events, such as DNA damage, replication stress, or mitotic spindle disruption. For example, DNA lesions and disrupted replication forks are recognized by the DNA damage checkpoint and replication checkpoint, respectively. Checkpoints can also, for example, initiate protein kinase-based signal transduction cascades to activate downstream effectors that elicit cell cycle arrest, DNA repair, or

apoptosis. These actions prevent the conversion of aberrant DNA structures into inheritable mutations and minimize the survival of cells with unrepairable damage (Qin and Li, 2003).

[0119] Dysregulation of the cell-cycle is a hallmark of tumor cells. Defective checkpoint function results in genetic modifications that contribute to tumorigenesis. Checkpoint function can be abrogated by many different mechanisms (Bast, et al., 2000). For example, cyclin-dependent kinases that normally are activated at a checkpoint can be inactivated or activated in an abnormal manner. Alternatively, the normal activities of the cyclin-dependent kinase inhibitors, phosphatases, or other regulatory molecules of the cell cycle can be altered. Tumor suppressors are among the classes of molecules that can effect cell cycle dysregulation. The abrogation of checkpoint function can alter the sensitivity of tumor cells to chemotherapeutics (Stewart et al, 2003).

[0120] Checkpoint-related sequences can possess or interact with phosphoribosylaminoimidazole-succinocarboxamide synthase (SAICAR\_synt) domains, which function in *de novo* purine synthesis ([http://pfam.wustl.edu/cgi-bin/getdesc?name=SAICAR\\_synt](http://pfam.wustl.edu/cgi-bin/getdesc?name=SAICAR_synt)). Checkpoint-related sequences can also possess or interact with WD40 domains, which comprise a domain of approximately 40 amino acids, which are sometimes present in tandem repeats (<http://pfam.wustl.edu/cgi-bin/getdesc?name=WD40>). Checkpoint-related sequences can also possess or interact with cyclin, C-terminal (cyclin\_C) domains, which regulate cyclin dependent kinases ([http://pfam.wustl.edu/cgi-bin/getdesc?name=cyclin\\_C](http://pfam.wustl.edu/cgi-bin/getdesc?name=cyclin_C)).

[0121] Thus, checkpoint related proteins, e.g., kinases, phosphatases, etc., are useful as targets for therapeutic intervention, such as in screening for small molecule drugs for the treatment of cancer, immune disorders, and inflammation.

### Complex-Related Sequences

[0122] Complexes are molecular entities comprised of two or more components. Molecular complexes within cells form functional units that carry out cellular operations. For example, complexes at the cell membrane perform structural and regulatory tasks, including regulating membrane traffic and maintaining organelle integrity. Complexes at the cytoskeleton perform static and dynamic roles with respect to cell shape, intracellular transport, and communication with the extracellular matrix. Complexes in the nucleus transcribe and regulate genes, and complexes at sites of protein synthesis translate and regulate proteins. Complexes can reside

intracellularly and/or extracellularly, e.g., in the extracellular matrix. Examples of complex-related sequences include cytoskeletal and filamentous proteins, ADP-ribosylation factor (ARF) proteins, and protein synthesis initiation factors (Amor et al., 1994).

[0123] Complex-related sequences can possess or interact with ADP-ribosylation factor family (arf) domains, which are GTP-binding domains involved in protein trafficking (<http://pfam.wustl.edu/cgi-bin/getdesc?name=arf>). Complex-related sequences can also possess or interact with eukaryotic initiation factor domains, e.g., the eukaryotic initiation factor 4E (IF4E) domain, which recognizes and binds mRNA during protein synthesis (<http://pfam.wustl.edu/cgi-bin/getdesc?name=IF4E>). Complex-related sequences can also possess or interact with intermediate filament (filament) protein domains, which form filamentous structures typically 8 to 14 nm wide, and form components of the cytoskeleton and nuclear envelope, e.g., neurofilaments, cytokeratins, lamins, vimentin, and desmin (<http://pfam.wustl.edu/cgi-bin/getdesc?name=filament>).

#### Cytokine-Related Sequences

[0124] A cytokine is an extracellular signaling protein or peptide that acts as a local mediator in communication among cells. Cytokines regulate proliferation and differentiation, for example, they mediate differentiation of cells in the hematopoietic lineage. Examples of cytokines include interleukins, interferons, and colony stimulating factors of the hematopoietic system. Some cytokines, e.g., interferons and interleukins, can be induced by viral activity, and possess antiviral activity (Sheppard et al., 2003). Cytokine-related sequences may enable the expression of a cytokine, for example, as a cytokine transcription factor (Kao et al., 1994). They can also be part of a cytokine effector pathway, for example, as an intracellular effector of cytokine-related cytoskeletal changes in response to events in the extracellular matrix (Hirsh et al., 2001; Joberty et al., 1999).

[0125] Cytokine-related sequences can possess or interact with interferon-induced transmembrane protein (CD225) domains, which are associated with interferon-induced cell growth suppression (<http://pfam.wustl.edu/cgi-bin/getdesc?name=CD225>). Cytokine-related sequences can also possess or interact with SeIR (SeIR) domains, which bind both selenium and zinc, and/or methionine sulfoxide reductase enzymatic domains (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SeIR>). Cytokine-related sequences can also possess or interact

with reverse transcriptase (rtv) domains, which are involved in RNA-directed DNA polymerase activity, an enzymatic activity that uses an RNA template to produce DNA for integration into a host genome (<http://pfam.wustl.edu/cgi-bin/getdesc?name=rtv>). Cytokine-related sequences can also possess or interact with L1 transposable element domains (Transposase\_22), which are described above.

[0126] Cytokines, thus, are useful as therapeutic proteins for the treatment of disorders such as cancer, immune disorders, and inflammation.

### **Dehydrogenase-Related Sequences**

[0127] Dehydrogenases are enzymes that catalyze the removal of hydrogen atoms in the absence of oxygen. They contribute to a wide range of enzymatic reactions, including those involved in amino acid degradation, amino acid synthesis, the citric acid cycle, fatty acid oxidation, fatty acid synthesis, glycolysis, the pentose phosphate pathway, photosynthesis, pyruvate oxidation, and oxidative phosphorylation (Walker et al., 1992). Examples of dehydrogenases include steroid dehydrogenases, NADH dehydrogenases, and glyceraldehyde-3-phosphate dehydrogenase.

[0128] Dehydrogenase-related sequences can possess or interact with glyceraldehyde 3-phosphate dehydrogenase, NAD binding (GPDH) domains, which play a role in glycolysis and gluconeogenesis by reversibly catalyzing the oxidation and phosphorylation of D-glyceraldehyde-3-phosphate to 1,3-diphospho-glycerate (<http://pfam.wustl.edu/cgi-bin/getdesc?name=gpdh>). Dehydrogenase-related sequences can also possess or interact with 3-hydroxyacyl-CoA dehydrogenase, NAD binding (3HCDH\_N) domains, which catalyze the reduction of 3-hydroxyacyl-CoA to 3-oxoacyl-CoA in fatty acid metabolism ([http://pfam.wustl.edu/cgi-bin/getdesc?name=3HCDH\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=3HCDH_N)).

### **Disease-Related Sequences**

#### *Amyotrophic Lateral Sclerosis*

[0129] Amyotrophic Lateral Sclerosis (Lou Gehrig's Disease) is a neurodegenerative disease that affects the motor neurons. The disease displays multiple clinical variants and can affect motor neurons throughout the nervous system, e.g., the spinal cord and brainstem. One clinical variant, the autosomal recessive form of juvenile amyotrophic lateral sclerosis, has been mapped to the human chromosome 2q33-q34 region (Hadano et al., 2001). A protein family characterized by the HAP1 N-terminal conserved region (HAP1\_N) domain possesses



a N-terminal conserved region from hypothetical protein products of ALS2CR3 genes found in the 2q33-2q34 region of chromosome 2 ([http://pfam.wustl.edu/cgi-bin/getdesc?name=HAP1\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=HAP1_N)).

#### *Gaucher's Disease*

[0130] Gaucher's Disease is a genetic disease characterized by a deficiency of enzymes responsible for the breakdown and recycling of glycolipids, i.e., lipids with carbohydrate moieties, e.g., glucosylceramide; and sphingolipids, lipids with sphingosine moieties, e.g., sphingomyelin. Normally, the glycolipids and sphingolipids in the membranes of senescent cells are metabolized by a multi-step process that includes the activities of acid beta-glucosidases and saposins. When these activities are absent, or present in reduced amounts, glucosylceramide and sphingolipids accumulate, and produce the Gaucher's disease phenotype. The disease displays multiple clinical variants, and can manifest with central nervous system pathology, enlargement of organs, e.g., liver and spleen, and an increase in the level of the cytokine transforming growth factor beta (Zhao and Grabowski, 2002; Perez Calvo et al., 2000; Cormand et al., 1997). The variability in clinical presentation is consistent with the large number of different mutations observed in the acid beta-glucosidase and saposin genes.

[0131] Acid beta-glucosidases are enzymes that metabolize glycolipids. Saposins are small proteins that are described in more detail below. Mammalian saposins are synthesized as a single precursor molecule (prosaposin) with saposin-A (SAPA) and saposin-B (SapB\_1; SapB\_2) domains; prosaposin becomes an active saposin following a proteolytic activation reaction (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SAPA>; [http://pfam.wustl.edu/cgi-bin/getdesc?name=SapB\\_1](http://pfam.wustl.edu/cgi-bin/getdesc?name=SapB_1); [http://pfam.wustl.edu/cgi-bin/getdesc?name=SapB\\_2](http://pfam.wustl.edu/cgi-bin/getdesc?name=SapB_2)).

#### *Huntington Disease*

[0132] Huntington Disease is a progressive neurodegenerative genetic disorder characterized by dementia, psychiatric symptoms, and a choreiform movement disorder. It is caused by an increased number of repeats of the codon CAG, which encodes the amino acid glutamine, in a gene located at the 4p16.3 region of chromosome 4, which codes for a protein called huntingtin. The polyglutamine tracts expressed by the mutant form of the gene selectively ablate striatal and cortical neurons, (Ho et al., 2001).

[0133] The Huntington Disease gene is widely expressed, but exerts tissue-specific effects on neurons (Lin et al., 1993). The gene expresses multiple distinct transcripts, and differential polyadenylation of the gene leads to the expression of transcripts of different sizes (Lin et al., 1993). There is a relative increase in the abundance of one transcript in the human brain, which has been hypothesized to account for the tissue-specific effects of the disease (Lin et al., 1993). The HAP1\_N protein domain, described above, binds to the gene product, huntingtin, in a polyglutamine repeat-length-dependent manner ([http://pfam.wustl.edu/cgi-bin/getdesc?name=HAP1\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=HAP1_N)). This domain is also found in several huntingtin-associated protein 1 (HAP1) homologues.

#### *Multiple Sclerosis (MS)*

[0134] Multiple sclerosis (MS) is a disease characterized by demyelination, i.e., the loss of the myelin coating, of nerve axons. Its clinical course varies among patients; these variations fall into two broad categories, a relapsing/remitting course, and a chronic progressive course. MS has a complex etiology; it has an autoimmune component, is influenced by genetics, and sometimes involves infectious agents. MS results from an abnormal immune response to one or more antigens present in the myelin sheaths that cover the nerve axons of genetically susceptible individuals, which may be preceded by exposure to a causal infectious agent (Oksenberg et al., 1999).

[0135] The genetic susceptibility to MS is determined by MS susceptibility genes, most of which demonstrate only a small to moderate effect on susceptibility, e.g., the major histocompatibility complex at chromosome 6p21 (Oksenberg et al., 1999). An etiological infectious agent has been isolated from the plasma and cerebrospinal fluid of patients with multiple sclerosis (Perron et al., 1997). This agent is a retroviral oncovirus, known as multiple sclerosis-associated retrovirus (MSRV), also called LM7, and is found in association with virions produced by the cultured cells of MS patients (Perron et al., 1997). MSRV proteins possess protein domains characteristic of retroviral proteins. These include the Gag P30 core shell protein (Gag\_p30) domain, which is involved in viral assembly ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Gag\\_p30](http://pfam.wustl.edu/cgi-bin/getdesc?name=Gag_p30)) and the reverse transcriptase (rvt) domain, which was described above.

### *Obesity*

[0136] Although single-gene mutations have been shown to cause obesity in animal models, the most common forms of human obesity arise from the interactions of multiple genes, environmental factors, and behavior. Several genes have been shown to affect body weight regulation in humans and other animals. These include the *ob*, *lep*, *CPE*, *ASIP*, *LEP*, *TUB*, *UPC*, *POMC*, *CCKAR*, *TNFA*, and *PPAR-γ* genes (Comuzzie et al., 1998). Genetic regulation of body weight can be effected through diverse mechanisms. For example, the *TUB* gene family regulates body weight by encoding proteins that are phosphorylated in response to insulin, mediate insulin signaling, and are associated with a maturity onset obesity associated with insulin resistance (Ikeda et al., 2002). *CCKAR* genes regulate body weight in a different manner; they regulate the hormone cholecystokinin, which produces a feeling of satiety following food intake (Ritter et al., 1994).

[0137] Some genes that regulate body weight possess the WHI domain, which is described above. Genes that regulate body weight can also possess or interact with the sprouty (sprouty) domain. This domain is found in sprouty proteins, which inhibit the Ras/mitogen-activated protein kinase cascade, a pathway initiated by receptor tyrosine kinases and involved in development (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Sprouty>). Genes that regulate body weight can also possess or interact with a Tub (Tub) domain, which is found in Tubby, a mouse gene in which an autosomal recessive mutation resulting from a splicing defect causes maturity-onset obesity, insulin resistance and sensory deficits (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Tub>).

### *Oncogene*

[0138] An oncogene is any one of a large number of genes that can help make a cell cancerous. Typically, an oncogene is a mutant form of a normal gene, and is often a gene involved in the control of cell growth, division, or differentiation. Cells in higher organisms normally grow, divide, differentiate, and die under the regulation of other cells. Cancer cells proliferate, in part, because they are able to divide without input from other cells, as the result of accumulated mutations. Oncogenes include, but are not limited to, genes encoding GTP binding proteins, e.g., *ras*; growth factors, e.g., platelet-derived growth factor; growth factor receptors, e.g.,

platelet-derived growth factor receptor; kinases, e.g., *src*; nuclear proteins, e.g., *myc*; and tumor suppressors, e.g., retinoblastoma proteins.

[0139] The products of oncogenes are frequently proteins involved in cell signaling, e.g., kinases, GTP-binding proteins, and receptors. For example, many human cancers have a mutation in a *ras* gene (Alberts et al., 1994). The *ras* proteins belong to a large superfamily of monomeric GTPases, and relay signals from receptor tyrosine kinases to the nucleus, stimulating cell proliferation or differentiation. *Ras* proteins function as switches, cycling between an active state in which GTP is bound, and an inactive state, in which GDP is bound. A *ras* gene mutation can result in the translation of a protein that fails to hydrolyze its bound GTP, and persists abnormally in its active state, transmitting an intracellular signal for cell proliferation or differentiation even in the presence of regulatory non-proliferation and non-differentiation signals. Oncogene-related proteins can possess one of many *ras* protein domains ([http://pfam.wustl.edu/cgi-bin/textsearch?terms=ras&search\\_what=all&sections=DE&sections=CC&size=100](http://pfam.wustl.edu/cgi-bin/textsearch?terms=ras&search_what=all&sections=DE&sections=CC&size=100)), including the sub-families *Ras*, *Rab*, *Rac*, *Ral*, *Ran*, *Rap*, and *Ypt1*. Oncogene-related proteins can also possess a *Gtr1/RagA* G-protein conserved region (*gtr1\_RagA*) domain, which is found in some G-proteins of the *Ras* family, e.g., the *RagA/B* human homologues of the *ras* GTP binding protein *Gtr1* ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Gtr1\\_RagA](http://pfam.wustl.edu/cgi-bin/getdesc?name=Gtr1_RagA)). Oncogene-related sequences can also possess or interact with an ATPase domain associated with diverse cellular activities; proteins with the AAA ('ATPases 'A' associated with diverse cellular 'A'ctivities) domain can perform chaperone-like functions that assist in assembling, operating, or disassembling protein complexes. The domain includes a conserved region of approximately 220 amino acids that contains an ATP-binding site which can act as an ATP-dependent protein clamp to hold a protein in place (<http://pfam.wustl.edu/cgi-bin/getdesc?name=AAA>). Some oncogene-related sequences can also possess or interact with a C2 domain of approximately 116 amino-acid residues, which can be involved in calcium-dependent phospholipid binding and inositol-1,3,4,5-tetraphosphate binding, and is found, e.g., in some isozymes of protein kinase C (<http://pfam.wustl.edu/cgi-bin/getdesc?name=C2>). C2 domains are typically located between C1 domains (which bind phorbol esters and diacylglycerol) and protein kinase catalytic domains. Regions with homology to the C2 domain are present in many proteins, e.g., synaptotagmin.

### *Parkinson's Disease*

[0140] Parkinson's disease is a neurological disorder that affects movement control. Complex interactions among groups of nerve cells in the central nervous system coordinate to control movement. One such group of neurons is located in the substantia nigra of the midbrain; these neurons release the neurotransmitter dopamine, which allows an organism to fine-tune its movements. In Parkinson's disease, neurons of the substantia nigra progressively degenerate, leaving the patient with clinical symptoms that may include resting tremor, muscular rigidity, a slowness of spontaneous movement, and poor balance and motor coordination (Seigel et al., 1999).

[0141] Parkinson's disease has multiple causes, including both genes and the environment. It also has multiple presentations, including juvenile-onset (before age 45) and adult onset (after age 45), and can be transmitted through either autosomal dominant or autosomal recessive mechanisms. In keeping with the diversity of etiologies, presentation, and genetic mechanisms, there are a large and diverse number of genes and gene products involved in the pathogenesis of Parkinson's disease. For example, the PARK2 gene, which encodes the protein parkin, is mutant in autosomal recessive juvenile parkinsonism. PARK2 is a ubiquitin protein ligase that is a component in the pathway that attaches ubiquitin to specific proteins, designating them for degradation (Fishman, and Oyler, 2002).

[0142] Parkinson's disease-related sequences can possess or interact with synuclein domains, which are expressed on the cytoplasmic regions of proteins found predominantly in neurons (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Synuclein>). Alpha-synuclein, which possesses a synuclein domain, is mutated in several families with autosomal dominant Parkinson's disease. Gamma-synuclein, which also possesses a synuclein domain, is overexpressed in breast and ovarian cancers (Lavedan, 1998).

### *Retinitis Pigmentosa*

[0143] Retinitis pigmentosa is a group of inherited retinopathies characterized by early stage loss of night vision, followed by loss of peripheral vision. Defects in any structural or functional proteins associated with the rod photoreceptor neurons of the retina, which are the cells that transduce light into a neuronal action potential, can lead to the disease (Seigel et al., 1999).

[0144] GTPase regulators have been implicated in the pathology of retinitis pigmentosa. GTPase regulators are proteins that determine whether a GTP binding protein exists in a GTP-bound or GDP-bound state (Zhao et al., 2003); they are described in more detail below. GTPase regulators have a broad spectrum of intracellular functions, including intracellular vesicular transport. These proteins localize to a specific region of rod photoreceptor cells, in a narrow cilium that connects the cell body, where protein synthesis and basic metabolism takes place, with the rod outer segment, where light is transduced to an action potential of the optic nerve (Zhao et al., 2003). Proteins necessary for the light transduction process are made in the cell body and must be transported to the outer segment via vesicular transport mechanisms. Mutant GTPase regulators, which regulate vesicular transport, play a role in the pathogenesis of retinitis pigmentosa (Roepman et al., 2000). Retinitis pigmentosa-related sequences can possess or interact with a Tctex-1 domain, which is comprised of a dynein light chain, and can bind to the cytoplasmic tail of rhodopsins, which are light-sensing proteins present in retinal rod cells (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Tctex-1>). Mutations in this domain that are responsible for retinitis pigmentosa inhibit this binding.

#### *Alzheimer's Disease*

[0145] Alzheimer's disease is a neurodegenerative dementing illness. It is a genetically complex disease with multiple forms, including familial and sporadic forms, and early onset and late-onset forms. Mutations in at least four genes are known to cause Alzheimer's disease, and there is evidence for additional Alzheimer's loci (McKusick, 2003). One form of Alzheimer's disease is caused by mutations in the amyloid precursor gene, another form is associated with the apolipoprotein E4 allele, a third form is caused by a mutant presenilin-1 gene that encodes a seven-transmembrane domain protein, and a fourth form is caused by a mutant gene encoding a similar seven-transmembrane domain protein, presenilin-2 (McKusick, 2003).

[0146] Consistent with its multiple etiologies, multiple clinical presentations, and multiple genetic loci, Alzheimer disease has a complex pathology. One facet of the pathology of Alzheimer's disease is the formation of amyloid plaques from amyloid precursor protein (Clark and Karlawish, 2003). Amyloid precursor protein can be processed *in vitro* by several different proteases such as secretases and caspases to yield peptide fragments, suggesting that these proteases may play a role in

the formation of pathogenic amyloid plaques *in vivo* (Suh and Checler, 2002). Presenilins have been identified as likely candidates for the proteases that cleave amyloid precursor protein to pathogenic peptide fragments *in vivo* (Selkoe, 2001). Another facet of Alzheimer's disease pathology is an inflammatory component mediated by microglial cells, the brain's primary immunoeffector cells (Tan et al., 1999). Microglial cells are attracted to and activated by amyloid deposits; they release inflammatory mediators that promote the aggregation of the deposits into plaques, and also directly induce or promote neurodegeneration (Hoozemans et al., 2002). Therefore, current treatment strategies include anti-inflammatory and immunotherapeutic approaches, including vaccines (Weiner and Selkoe, 2002).

[0147] Alzheimer's disease-related sequences can possess or interact with trypsin domains, which demonstrate a wide range of peptide degrading activities, including exopeptidase, endopeptidase, oligopeptidase and omega-peptidase activities (<http://pfam.wustl.edu/cgi-bin/getdesc?name=trypsin>). Alzheimer's disease-related sequences can also possess or interact with low-density lipoprotein receptor (ldl\_rece) domains, which are characterized by seven successive cysteine-rich repeats of about 40 amino acids at the N-terminal region, and which are also present in receptors for low density lipoprotein (LDL), the major cholesterol-carrying lipoprotein of plasma ([http://pfam.wustl.edu/cgi-bin/textsearch?terms=ldl\\_rece+%&search\\_what=all&sections=DE&sections=CC&size=100](http://pfam.wustl.edu/cgi-bin/textsearch?terms=ldl_rece+%&search_what=all&sections=DE&sections=CC&size=100)). Alzheimer's disease-related sequences can also possess or interact with a PT repeat (pt\_a) domain, which includes the tetrapeptide XPTX, or a similar, conserved, sequence.

#### *Williams-Beuren Syndrome*

[0148] Williams-Beuren syndrome is a complex genetic developmental disorder with multisystemic manifestations, and variability in its presentation. In 90-95% of the cases reported, a gene deletion occurs at the 7q11.23 location on the long arm of chromosome 7; in the remaining cases, a variety of other chromosomal deletions and translocations have been observed (Wang et al., 1999). The most severe cases are characterized by cardiac anomalies, including aortic stenosis, mental retardation, growth deficiency, a characteristic facial appearance, dental malformation, and infantile hypercalcemia (Lashkari et al., 1999).

[0149] The underlying molecular basis for the syndrome is the absence of the proteins encoded by the genes of the affected region of the chromosome. A missing elastin gene, with resulting extracellular matrix anomalies, is a consistent

finding. Other genes that are present in and near the commonly deleted region of chromosome 7, and thus are likely to contribute to pathogenesis, are (1) a gene encoding a regulator of chromosome condensation-like G-exchanging factor, which is a factor that exchanges nucleotides for small GTP-binding proteins, (2) an N-acetylgalactosaminyltransferase, (3) a DNAJ-like chaperone, (4) NOL1/NOP2/sun domain-containing proteins, including a novel protein designated WBSCR20, which is expressed in skeletal muscle, and is similar to a 120 kilodalton proliferation-associated nucleolar antigen, (5) a methyltransferase designated WBSCR22, and (6) other proteins with no known homologies (Merla et al., 2002; Doll and Grzeschik, 2001). Williams-Beuren-related sequences can possess or interact with a GTF2I-like repeat (GTF2I) domain, which is a DNA binding domain commonly deleted in Williams-Beuren syndrome, (<http://pfam.wustl.edu/cgi-bin/getdesc?name=GTF2I>).

#### *Rheumatic Diseases*

[0150] Rheumatic diseases are inflammatory conditions that can have autoimmune, infective, or traumatic origins. They include arthritis, systemic lupus erythematosus, scleroderma, and Sjogren's syndrome. Arthritis refers to any inflammation of a joint. Systemic lupus erythematosus is an autoimmune disease in which patients produce antibodies to their own tissues, resulting in an inflammatory process that can damage organs. Scleroderma can present as systemic scleroderma, a chronic, progressive disease that is characterized by hardening and stiffening of the skin and damage to internal organs, e.g., heart, lungs, kidneys and esophagus. Sjogren's syndrome is a progressive immunological disorder characterized by inflammation and the subsequent destruction of exocrine glands, e.g., salivary glands, sweat glands, and lacrimal (tear) glands.

[0151] The serum of patients with scleroderma and Sjogren's syndrome have antibodies directed against a protein that is a normal component of the Golgi apparatus (Seelig et al., 1994), an intracellular organelle composed of a stack of flattened cisternae with associated transport vesicles. The Golgi apparatus sorts proteins and sends them to their correct intracellular destination. This antigenic protein is a "golgin," one of a class of molecules characterized by an integral membrane domain and a large cytoplasmic region. Golgins organize the Golgi's structure, and influence protein sorting (Gillingham et al., 2002). Golgins function in a variety of ways, including cross-bridging Golgi cisternae to one another (Linstedt and Hauri, 1993) and tethering Golgi transport vesicles to the cisternal membranes



(Shorter et al., 2002). Rheumatic disease-associated sequences can possess or interact with golgin-97, RanBP2alpha, Imh1p, and p230/golgin (GRIP) domains, which are found in many large coiled-coil proteins, are sufficient for targeting to the Golgi, and have a conserved tyrosine residue (<http://pfam.wustl.edu/cgi-bin/getdesc?name=GRIP>).

#### **Disintegrin-Related Sequences**

[0152] Disintegrins are proteins that interfere with the function of integrins. Disintegrins are generally proteins of about 70 amino acid residues that contain multiple disulfide bonds, bind with high affinity to a subset of integrins, and interfere with integrin binding to physiological ligands. Examples of disintegrin-related sequences include snake venoms and related proteins, cysteine-rich metalloproteinases and related non-enzymatic sequences, e.g., those expressed in the male reproductive tract, and membrane-anchored metalloproteinases with diverse functions, e.g., the shedding of cell-surface proteins such as cytokines and cytokine receptors, and the conferring of asthma susceptibility (Van Eerdewegh et al., 2002; Perry et al., 1995).

[0153] Disintegrin-related sequences can possess or interact with disintegrin domains, which contain an Arg-Gly-Asp sequence, a sequence commonly found in adhesion proteins (<http://pfam.wustl.edu/cgi-bin/getdesc?name=disintegrin>). Proteins that comprise both disintegrin and metalloproteinase peptidase domains include ADAM proteins. Disintegrin-related sequences can also possess or interact with repolysin family propeptide (Pep\_M12B\_propep) domains, which are domains that include the propeptide sequence of members of the peptidase family M12B, and contain a sequence motif similar to a sequence found in matrixin proteins ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Pep\\_M12B\\_propep](http://pfam.wustl.edu/cgi-bin/getdesc?name=Pep_M12B_propep)).

#### **Factor-Related Sequences**

[0154] A factor is any molecule that contributes to a bodily process. Factors can function in specific biochemical reactions and cellular functions. There are many categories of factors, and factors are involved in many, if not all, physiological and pathological processes. Some exemplary factors are described in the following paragraphs; they are not exhaustive of the category.

[0155] Transcription factors are factors that initiate or regulate transcription in eukaryotes. They include gene regulatory proteins, which turn specific sets of genes on or off, and general transcription factors, which assemble at the promoter

region to enable and regulate transcription of many genes. They also include transcription elongation factors, which are proteins required for the addition of amino acids to growing polypeptide chains on ribosomes (Alberts et al., 1994). Transcription factors interact with a wide variety of molecules, including DNA binding proteins, polymerases, regulatory molecules such as kinases, and specific regions of DNA, e.g., promoters, and enhancers (Alberts et al., 1994; Vallejo et al., 1993).

[0156] Translation factors, including translation initiation factors and release factors, are involved in initiating and regulating the rate of protein synthesis. They also interact with many molecules, including ribosomal proteins, mRNA, and molecules that regulate the incorporation of amino acids into protein, such as kinases and GTP (Price et al., 1993; Alberts, 1994).

[0157] Export factors are involved in the export of molecules, e.g., RNA, from the nucleus (Stutz et al., 2000). Folding factors are involved in the process of folding proteins into their functional three dimensional shapes, and are also involved in receptor function (Gao et al., 1994). Factors such as activators and coactivators interact with nuclear receptors to modulate cellular processes, e.g., transcription (Mahajan et al., 2002).

[0158] ADP-ribosylation factors are involved in the addition of an ADP-ribose group donated from nicotinamide adenine dinucleotide (NAD) to specific amino acid residues in heterotrimeric G-proteins. They are involved in, for example, normal cellular processes, such as vesicular transport, and also in the pathologic states induced by cholera, pertussis, and botulinum toxins (Alberts et al., 1994; Amor et al., 1994). Guanine nucleotide exchange factors bind to small G-proteins, such as Ras, and displace GDP in favor of GTP. They act as effectors or modulators of small G-proteins (Ehrhardt et al., 2001; Janeway et al., 2001; Shao and Andres, 2000).

[0159] Factor-related sequences can possess or interact with ADP-ribosylation factor family (arf) domains, which are GTP-binding domains involved in protein trafficking (<http://pfam.wustl.edu/cgi-bin/getdesc?name=arf>). Factor-related sequences can also possess or interact with elongation factor Tu GTP binding (GTP\_EFTU) domains, which are elongation factors that promote the GTP-dependent binding of aminoacyl tRNA to ribosomes during protein biosynthesis, and catalyze the translocation of the newly synthesised protein chain ([http://pfam.wustl.edu/cgi-bin/getdesc?name=GTP\\_EFTU](http://pfam.wustl.edu/cgi-bin/getdesc?name=GTP_EFTU)). Factor-related sequences can also possess or

interact with 4F5 protein family (4F5) domains, which comprise ubiquitously expressed short proteins rich in aspartate, glutamate, lysine and arginine (<http://pfam.wustl.edu/cgi-bin/getdesc?name=4F5>). Factor-related sequences can also possess or interact with eukaryotic initiation factors, e.g., eukaryotic initiation factor 4E (IF4E), which recognizes and binds mRNA during an early step of protein synthesis (<http://pfam.wustl.edu/cgi-bin/getdesc?name=IF4E>).

#### **Germ Cell Specific Protein-Related Sequences**

[0160] Germ cells, also called gametes, are cells that contribute to a new generation of organisms by giving rise to either an egg or a sperm. They are haploid cells specialized for sexual fusion. Proteins that are specific to germ cells can be found at one or more developmental stages of gametes.

[0161] Germ cell-related sequences include germ cell genes and their gene products, their regulators and effectors, genes and gene products affected in disorders associated with germ cells, and antibodies that specifically recognize or modulate germ cell-related sequences. Examples of germ cell-related sequences include the germ cell-specific Y-box binding protein and contrin. Germ cell specific protein-related sequences possess or interact with the cold-shock DNA-binding (CSD) domain, which is described above.

#### **Growth Factor-Related Sequences**

[0162] A growth factor is an extracellular polypeptide signaling molecule that stimulates a cell to grow or proliferate. Many types of growth factors exist, including protein hormones and steroid hormones. Some growth factors have a broad specificity, and some have a narrow specificity. Examples of growth factors with broad specificity include platelet-derived growth factor, epidermal growth factor, insulin like growth factor I, transforming growth factor  $\beta$ , and fibroblast growth factor, which act on many classes of cells. Examples of growth factors with narrow specificity include erythropoietin, which induces proliferation of precursors of red blood cells, interleukin-2, which stimulates proliferation of activated T-lymphocytes, interleukin-3, which stimulates proliferation and survival of various types of blood cell precursors, and nerve growth factor, which promotes the survival and the outgrowth of nerve processes from specific classes of neurons.

[0163] Most growth factors have other actions in addition to inducing cell growth or proliferation, e.g., they may influence survival, differentiation, migration,

or other cellular functions. Growth factors can have complex effects on their targets, e.g., they may act on some cells to stimulate cell division, and on others to inhibit it. They may stimulate growth at one concentration, and inhibit it at another. Growth factors are also involved in tumorigenesis.

[0164] Growth factor related sequences include sequences associated with the process of stimulating cell growth or proliferation by a growth factor. For example, they include intracellular effectors of growth, such as components of intracellular pathways that respond to growth factors (Kothapalli et al., 1997; Wax et al., 1994), sequences that bind directly or indirectly to growth factors (Van den Berghe et al., 2000), and sequences affected as a result of growth factor action.

[0165] Growth factor-related sequences can possess or interact with a transforming growth factor beta like (TGF-beta) domain, which is a multifunctional peptide sequence that controls proliferation, differentiation and other functions in many cell types (<http://pfam.wustl.edu/cgi-bin/getdesc?name=TGF-beta>). Growth factor-related sequences can also possess or interact with a fibroblast growth factor (FGF) domain, which is found in a family of proteins involved in growth and differentiation (<http://pfam.wustl.edu/cgi-bin/getdesc?name=FGF>).

#### **GTPase-Related Sequences**

[0166] GTPases are enzymes that catalyze GTP hydrolysis, and comprise a large family of proteins with a similar globular GTP binding domain. When GTP is bound to a GTPase, it is hydrolyzed to GDP, and the domain undergoes a conformational change that inactivates the protein. GTPases are regulated by GTPase regulators, proteins that determine whether a GTP binding protein exists in a GTP-bound or GDP-bound state (Zhao et al., 2003). GTPase regulators include GTPase activating proteins, which bind the GTPase and induce it to hydrolyze its bound GTP to GDP; the GTPase remains in an inactive, GDP-bound state until it encounters a guanine nucleotide releasing protein, which binds to the GTPase and causes the release of the nucleotide. GTPases have a broad spectrum of intracellular functions, including intracellular vesicular transport. Examples of GTPase-related sequences include ras, GTPase-activating proteins, and guanine nucleotide releasing proteins.

[0167] GTPase-related sequences can possess or interact with GTPase activator protein for Ras-like GTPase (RasGAP) domains, which are protein domains of about 250 residues that accelerate the GTPase activity of ras

(<http://pfam.wustl.edu/cgi-bin/getdesc?name=RasGAP>). GTPase-related sequences can also possess or interact with putative GTPase activating protein for ARF (ArfGAP) domains, which are protein domains with a zinc finger involved in intermolecular associations (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ArfGAP>). GTPase-related sequences can also possess or interact with ankyrin repeat domains (ank), which are tandemly repeated modules of about 33 amino acids found in a variety of functionally diverse proteins (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ank>). GTPase-related sequences can also possess or interact with pleckstrin homology (PH) domains, which are protein domains of about 100 residues involved in intracellular signaling, or as components of the cytoskeleton (<http://pfam.wustl.edu/cgi-bin/getdesc?name=PH>).

### Heat-Shock Protein-Related Sequences

[0168] Heat-shock proteins, also referred to as stress-response proteins, are proteins that are synthesized in response to an elevated temperature or other cell stressor, and help the cell withstand environmental insults. A cell stressor can induce a battery of genes that encode gene products that protect the cell from the result of the insult, e.g., proteins that stabilize and repair partially denatured cell proteins. Some heat-shock proteins, e.g., chaperones, are present at high levels in unstressed cells, and further induced by stress. Chaperones assist other proteins in attaining their proper secondary and tertiary structures. For example, members of the tubulin-specific chaperone A family possess tubulin-specific chaperone A (TBCA) domains that fold tubulin polypeptides into their functional configuration (<http://pfam.wustl.edu/cgi-bin/getdesc?name=TBCA>).

[0169] Heat and other stressors further induce the synthesis of a family of 90-kDa heat-shock proteins that are already abundant in unstressed cells (Pepin et al., 2001; Lees-Miller et al., 1989; Rebbe et al., 1987). Members of this family possess a hsp 90 protein (HSP90) domain that interacts with tubulin, actin, tyrosine kinase oncogene products of retroviruses, cF2alpha kinase, and steroid hormone receptors (Lees-Miller and Anderson, 1989). This domain includes a highly-conserved N-terminal region, separated from a conserved, acidic C-terminal region by a highly-acidic, flexible linker region (<http://pfam.wustl.edu/cgi-bin/getdesc?name=HSP90>).

[0170] Another family of heat-shock proteins, the hsp70 proteins, have an average molecular weight of 70 kDa; some members of this family are only expressed under conditions of stress, while some are present in cells under normal conditions. Hsp70 proteins reside in different cellular compartments, e.g., the nucleus, cytosol,

mitochondria, and endoplasmic reticulum. Hsp70 proteins, e.g., Hsc73, can be differentially expressed at different stages of development (Soulier et al., 1996). Hsp70 proteins, e.g., the chaperone hsp70-like dnaK protein, can associate with proteins that possess a DnaJ domain, which comprises an N-terminal conserved domain of about 70 amino acids, a glycine-rich region of about 30 amino acids, a central domain containing four repeats of a CXXCXGXX motif, and a C-terminal region of 120 to 170 amino acids (<http://pfam.wustl.edu/cgi-bin/getdesc?name=DnaJ>). Proteins with DnaJ domains can be postrationally modified by farnesylation (Andres et al., 1997).

### **Helicase-Related Sequences**

[0171] Helicases are enzymes that use energy from the hydrolysis of ATP to unwind the DNA helix at the replication fork, allowing the single strands to be copied. Proteins with DNA helicase activity play roles in DNA replication, repair, and recombination. Disorders associated with helicases include Xeroderma pigmentosum, Cockayne syndrome, diffuse collagen disease, alpha-thalassemia, Bloom syndrome, Werner syndrome, and Rothmund-Thomson syndrome (Miyajima, 2002). Examples of helicases include RNA helicases, RECQL4, and minichromosome maintenance helicase.

[0172] Helicase-related sequences can possess or interact with helicase associated (HA) domains, which are protein domains comprising alpha helices that may bind to nucleic acids (<http://pfam.wustl.edu/cgi-bin/getdesc?name=HA>). Helicase-related sequences can also possess or interact with helicase conserved C-terminal (helicase\_C) domains, which are protein domains that are found in a subset of helicases designated the DEAD/H helicases ([http://pfam.wustl.edu/cgi-bin/getdesc?name=helicase\\_C](http://pfam.wustl.edu/cgi-bin/getdesc?name=helicase_C)).

### **Hydrolase-Related Sequences**

[0173] Hydrolases are enzymes that catalyze the hydrolysis of a variety of bonds, such as esters, glycosides, and peptides. Hydrolases split a molecule into fragments by adding water; the water's hydrogen atom is incorporated into one fragment, and the hydroxyl group is incorporated into another. Hydrolases are involved in a wide range of physiological and pathological processes, including proteolysis, phosphatase activity, and sugar metabolism. Examples of hydrolases include protein hydrolases, lipid hydrolases, nucleic acid hydrolases, and small molecule, e.g., coenzyme A, hydrolases (Hawes et al., 1996).

[0174] Hydrolase-related sequences can possess or interact with alpha/beta hydrolase fold (abhydrolase) domains, which are catalytic domains found in a wide range of hydrolytic enzymes of different phylogenetic origins and catalytic functions (<http://pfam.wustl.edu/cgi-bin/getdesc?name=abhydrolase>). Hydrolase-related sequences can also possess or interact with dUTPase domains, which are proteins domains that hydrolyze dUTP to dUMP and pyrophosphate.

#### **Immune Cell-Related Sequences**

[0175] An immune cell is a cell involved in, or associated with, the immune system. Immune cells include cells in the myeloid and lymphocytic arms of the immune response, as well as their precursors. Immune cells also include cells at all stages in the differentiation pathways that produce cells associated with the immune system. These cells can reside, either permanently or temporarily, in the spleen, lymph nodes or mucosal-associated lymphoid tissues (MALT). Immune cell-related sequences are involved in all functions of the immune response, e.g., antibody production and cell-mediated immunity, and can function at any point in time, ranging from the embryonic formation of the immune system, through the time of an immune challenge, to many decades later, e.g., when a B-cell memory response is invoked (Janeway, 2001).

[0176] Immune-cell related sequences of differentiating immune cells include pre-B cells that do not produce immunoglobulin light chain, but express a transcript homologous to immunoglobulin lambda light-chain genes, the expression of which is limited to pre-B cells and select other cells that have no surface immunoglobulin (Hollis et al., 1989). Immune-cell related sequences of activated immune cells include a B-cell-restricted transcription factor expressed by activated B cells; its expression pattern suggests it has a role in regulating B-cell differentiation (Massari et al., 1998).

[0177] Examination of the expression of immune-cell related sequences can detect and diagnose immunoregulatory abnormalities. For example, genes that encode proteins which mediate the combinatorial process that combines a finite number of component genes into the very broad range of antigen-specific immunoglobulin and T-cell binding proteins, are expressed at higher levels in patients with systemic lupus erythematosus (SLE) than in healthy subjects (Girschick et al., 2002).

[0178] Immune cell-related sequences can possess or interact with a CUB domain, which is an extracellular domain of approximately 110 amino acids, and is present in functionally diverse, including developmentally regulated, proteins (<http://pfam.wustl.edu/cgi-bin/getdesc?name=CUB>). Immune cell-related sequences can also possess or interact with a CD-20 domain, which has four transmembrane regions, both extracellular and cytoplasmic extensions, and is found, inter alia, in a high affinity IgE receptor (<http://pfam.wustl.edu/cgi-bin/getdesc?name=CD20>). Immune cell-related sequences can also possess or interact with an interferon-induced transmembrane protein (CD225) domain, which is found in a family of proteins that includes the human leukocyte antigen CD225, an interferon-inducible transmembrane protein associated with interferon-induced cell growth suppression (<http://pfam.wustl.edu/cgi-bin/getdesc?name=CD225>). Immune cell-related sequences can also possess or interact with sushi domains, also known as complement control protein (CCP) modules, or short consensus repeats (SCR). These domains are found in a wide variety of complement and adhesion proteins, including proteins responsible for the antigenicity of blood group antigens on the external face of the red blood cell membrane (<http://pfam.wustl.edu/cgi-bin/getdesc?name=sushi>). Immune cell-related sequences can also possess or interact with SH2 domains and rvt domains; both are described above.

#### **Integrase-Related Sequences**

[0179] Integrases are enzymes that form proviruses by inserting a linear double-stranded DNA copy of a retroviral genome into host cell DNA. Examples of integrases include HIV integrase, PhiC31 integrase, and Sip.

[0180] Integrase-related sequences can possess or interact with an integrase zinc binding domain (Integrase\_Zn) domain, which is a zinc binding protein domain placed near the N-terminus ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Integrase\\_Zn](http://pfam.wustl.edu/cgi-bin/getdesc?name=Integrase_Zn)). Integrase-related sequences can also possess or interact with an integrase core (rve) domain, which is a protein domain that forms the central catalytic core of the integrase (<http://pfam.wustl.edu/cgi-bin/getdesc?name=rve>). This domain acts as an endonuclease to cleave the nucleotide and catalyzes the transfer of the viral DNA strand to the integration site of the host DNA. Integrase-related sequences also possess or interact with an integrase DNA binding (integrase) domain, which is a DNA-binding protein domain near the C-terminus (<http://pfam.wustl.edu/cgi-bin/getdesc?name=integrase>). Integrase-related sequences also possess or interact



reverse transcriptase (rtv) domains, which are described above. Integrase-related sequences also possess or interact with a RNase H domain, which is a protein domain that hydrolyzes the RNA portion of RNA/DNA hybrids (<http://pfam.wustl.edu/cgi-bin/getdesc?name=rnaseH>).

### **Integrin-Related Sequences**

[0181] Integrins are transmembrane proteins that mediate cell to cell as well as cell to matrix adhesion, and provide a means of communication between the interior of a cell and the extracellular matrix. The extracellular portion of integrins binds to components of the extracellular matrix, e.g., collagen, fibronectin and laminin. The intracellular portion of integrins interacts with the cell cytoskeleton, e.g., actin filaments near the cell surface. Integrins transmit information about the extracellular environment across the plasma membrane to the cytoskeleton, where it is available to intracellular signaling mechanisms (Alberts et al., 1994). Structurally, integrins consist of heterodimers of an alpha and a beta subunit. Each subunit has a large N-terminal extracellular domain followed by a transmembrane domain and a short C-terminal cytoplasmic region. The pairing of certain alpha subunits with certain beta-subunits determines ligand specificity, localization and function. The extracellular binding domains of integrins often bind their ligands with low affinity; simultaneous, weak, binding with multiple matrix molecules provides the cell with a means to sense its complex, changing, extracellular environment without becoming glued to it. Examples of integrin-related sequences include integrin alpha and beta subunits, collagens, and integrin-linked kinase (Zhang et al., 2002).

[0182] Integrin-related sequences can possess or interact with von Willebrand factor type A (vwa) domains, which are protein domains that participate in diverse biological functions, e.g., cell adhesion, migration, homing, pattern formation, and signal transduction (<http://pfam.wustl.edu/cgi-bin/getdesc?name=vwa>). Integrin-related sequences can also possess or interact with FG-GAP repeat (FG-GAP) domains, which are protein domains present in the vicinity of ligand binding domains at the N-terminus of integrin alpha subunits (<http://pfam.wustl.edu/cgi-bin/getdesc?name=FG-GAP>).

### **Interacting Protein-Related Sequences**

[0183] An "interacting protein" is a protein that interacts with another molecule. Interacting proteins are involved in every aspect of cellular function. Interacting proteins have been characterized in all known locations in the cell, and

include all, or most types of, proteins. Interacting proteins in the nucleus regulate such diverse functions as apoptosis, transcription, homologous recombination, and DNA repair. Nuclear fibroblast growth factor-2 interacting factor interacts with fibroblast growth factor 2 to prevent apoptosis (Van den Berghe et al., 2000). Grap2 cyclin-D interacting protein (GCIP) a nuclear cell-cycle protein, inhibits select transcriptional events, and reduces the level of phosphorylation of nuclear retinoblastoma protein (Chang et al., 2000). Pir 51, a human homologue of Rec A, a bacterial enzyme that mediates genetic recombination, interacts with the enzyme rad51 to regulate homologous recombination and DNA repair in mammalian cells (Kovalenko et al., 1997). Hepatitis B virus X-associated protein (HBXAP), a protein demonstrated to play a role in the development of hepatocellular carcinoma, interacts with the hepatitis B virus regulatory gene product HBx to increase viral transcription (Shamay et al., 2002).

[0184] Interacting protein-related proteins can utilize many protein domain motifs for interaction. They can possess or interact with domains that mediate interaction with DNA, RNA, ions, or other proteins. For example, PDZ domains, which are also known as DHR or GLGF domains, target signaling molecules to membranes and mediate the assembly of functional membrane domains (Fanning and Anderson, 1999). Interacting protein-related proteins can also possess or interact with rrm domains, which are described above.

#### **Isomerase-Related Sequences**

[0185] Isomerases are enzymes that convert molecules into their positional isomers, i.e., into molecules with the same chemical formula but a different stereochemical arrangement of atoms. Isomerases act on a wide variety of molecules, including sugars, amino acids, and nucleic acids. They are involved in a wide range of physiological and pathological functions, including those involving metabolic and synthetic pathways.

[0186] Isomerase-related sequences include isomerase genes and gene products, their substrates, products, activators, inhibitors, effectors, and cofactors, regulatory molecules that modulate their function, genes and gene products affected in disorders associated with isomerases and antibodies that specifically recognize or modulate isomerase-related sequences. Examples of isomerase-related sequences include triosephosphate isomerases, peptidyl-prolyl isomerases, glucose phosphate

isomerases, disulfide isomerases, ketosteroid isomerases, and ribosyltransferase-isomerases (Brown et al., 1985).

[0187] Isomerase-related sequences can possess or interact with triosephosphate isomerase (TIM) domains, which are protein domains that catalyze the reversible interconversion of glyceraldehyde 3-phosphate and dihydroxyacetone phosphate (<http://pfam.wustl.edu/cgi-bin/getdesc?name=TIM>). Isomerase-related sequences can also possess or interact with cyclophilin type peptidyl-prolyl cis-trans isomerase (pro\_isomerase) domains, which accelerate protein folding by catalyzing the cis-trans isomerization of peptide bonds ([http://pfam.wustl.edu/cgi-bin/getdesc?name=pro\\_isomerase](http://pfam.wustl.edu/cgi-bin/getdesc?name=pro_isomerase)).

#### **Mucin-Related Sequences**

[0188] The term mucin refers to both an albumin-like substance that is present in mucus, and to transmembrane proteins that can typically be produced in both soluble and transmembrane forms. Soluble mucins comprise mucus gels that protect epithelial cells in the airways, digestive tract, and other organs, and are found in body fluids, such as milk, tears, and saliva. In their transmembrane forms, mucins provide a steric barrier to protect the apical surface of epithelial cells. Transmembrane mucins are also involved in pathogenesis; for example, they mediate viral entry into cells, promulgate the inflammatory response, and are involved in the regulation of abnormal cell proliferation (Jeffery and Zhu, 2002; Tsuda et al., 1993). Examples of mucins include MUC2 mucin, mucin carcinoembryonic antigen, and Muc3 membrane bound intestinal mucin.

[0189] Mucin-related sequences can possess or interact with mucin-like glycoprotein (tryp\_mucin) domains, which are domains that are involved in the interaction of parasites with host cells ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Tryp\\_mucin](http://pfam.wustl.edu/cgi-bin/getdesc?name=Tryp_mucin)). Mucin-related sequences can also possess or interact with multi-glycosylated core protein (MGC-24) domains, which are protein domains of sialomucins that are expressed in many normal and cancerous tissues (<http://pfam.wustl.edu/cgi-bin/getdesc?name=MGC-24>).

#### **Other Polypeptide-Related Sequences**

[0190] In addition to the sequences described above, the sequences of the invention include nucleotide and amino acid sequences, some with known function, and some with unknown function, that fall into a broad array of categories.

[0191] Polypeptide-related sequences of the invention can possess or interact with groucho/TLE N-terminal Q-rich (TLE\_N) domains, which are protein domains found in co-repressor proteins, and are involved in oligomerization ([http://pfam.wustl.edu/cgi-bin/getdesc?name=TLE\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=TLE_N)). Polypeptide-related sequences of the invention can also possess or interact with uncharacterized protein family 0160 (UPF0160) domains, which are protein domains found in proteins that include multiple metal-binding residues, and in some cases act as a phosphodiesterase (<http://pfam.wustl.edu/cgi-bin/getdesc?name=UPF0160>). Polypeptide-related sequences of the invention can also possess or interact with SNF7 domains, which are protein domains involved in protein sorting and transport from the endosome to the lysosome or vacuole of eucaryotic cells (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SNF7>). Polypeptide-related sequences of the invention can also possess or interact with NifU-like N-terminal (NifU\_N) domains, which are protein domains involved in nitrogen fixation, and other functions ([http://pfam.wustl.edu/cgi-bin/getdesc?name=NifU\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=NifU_N)). Polypeptide-related sequences of the invention can also possess or interact with tRNA synthetases class II (D, K, and N) (tRNA-synt\_2) domains, which are protein domains that activate the amino acids asparagines, aspartic acid, and lysine, and transfer them to specific tRNA molecules ([http://pfam.wustl.edu/cgi-bin/getdesc?name=tRNA-synt\\_2](http://pfam.wustl.edu/cgi-bin/getdesc?name=tRNA-synt_2)).

[0192] Polypeptide-related sequences of the invention can also possess or interact with dynein heavy chain (dynein\_heavy) domains, which are protein domains that correspond to the C-terminal region of the dynein heavy chain ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Dynein\\_heavy](http://pfam.wustl.edu/cgi-bin/getdesc?name=Dynein_heavy)). Polypeptide-related sequences of the invention can also possess or interact with cyclin-dependent kinase regulatory subunit (CKS) domains, which are protein domains of approximately 79-150 amino acid residues that are involved in regulating progression through the cell cycle (<http://pfam.wustl.edu/cgi-bin/getdesc?name=CKS>).

[0193] Polypeptide-related sequences of the invention can also possess or interact with nucleoside diphosphate linked to some other moiety X (NUDIX) domains, which are protein domains that are involved in removing oxidatively damaged nucleotides (<http://pfam.wustl.edu/cgi-bin/getdesc?name=NUDIX>). Polypeptide-related sequences of the invention can also possess or interact with T-complex protein/cpn60 chaperonin (cpn60\_TCP1) domains, which are protein domains involved in protein folding and oligomerization (<http://pfam.wustl.edu/cgi->

bin/getdesc?name=cpn60\_TCP1). Polypeptide-related sequences of the invention can also possess or interact with F-actin capping protein, beta subunit (F\_ actin\_cap\_B) domains, which are protein domains of approximately 280 amino acids that are involved in capping actin, i.e., blocking the exchange of actin monomers ([http://pfam.wustl.edu/cgi-bin/getdesc?name=F\\_ actin\\_cap\\_B](http://pfam.wustl.edu/cgi-bin/getdesc?name=F_ actin_cap_B)).

[0194] Polypeptide-related sequences of the invention can also possess or interact with G-protein alpha subunit (G-alpha) domains, which are protein domains that bind guanyl nucleotides, and function as a GTPase (<http://pfam.wustl.edu/cgi-bin/getdesc?name=G-alpha>). Polypeptide-related sequences of the invention can also possess or interact with Kruppel-associated box (KRAB) domains, which are protein domains involved in protein-protein interactions, and present in some zinc finger proteins (<http://pfam.wustl.edu/cgi-bin/getdesc?name=KRAB>). Polypeptide-related sequences of the invention can also possess or interact with metallopeptidase family M24 (Peptidase\_M24) domains, which are protein domains that are found in some metalloproteases, including proline dipeptidase, and methionine aminopeptidase ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Peptidase\\_M24](http://pfam.wustl.edu/cgi-bin/getdesc?name=Peptidase_M24)). Polypeptide-related sequences of the invention can also possess or interact with thioredoxin (thioered) domains, which are protein domains involved in oxidation/reduction reactions by reversibly oxidizing disulfide bonds (<http://pfam.wustl.edu/cgi-bin/getdesc?name=thioered>).

[0195] Polypeptide-related sequences of the invention can also possess or interact with TUDOR domains, which are protein domains involved in the formation of primordial germ cells, and for normal abdominal segmentation (<http://pfam.wustl.edu/cgi-bin/getdesc?name=TUDOR>). Polypeptide-related sequences of the invention can also possess or interact with SIT4 phosphatase-associated protein (SAPS) domains, which are protein domains that are involved in cyclin transcription (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SAPS>). Polypeptide-related sequences of the invention can also possess or interact with ankyrin repeat (ank) domains, which are protein domains of approximately 33 amino acids, and are sometimes found in tandemly repeated modules (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ank>). Polypeptide-related sequences of the invention can also possess or interact with nicotinamide N-methyltransferase/phenylethanolamine N-methyltransferase/thioether S-methyltransferase (NNMT\_PNMT\_TEMT) domains, which are protein domains that are found in proteins that use S-adenosyl-L-

methionine as the methyl donor ([http://pfam.wustl.edu/cgi-bin/getdesc?name=NNMT\\_PNMT\\_TEMT](http://pfam.wustl.edu/cgi-bin/getdesc?name=NNMT_PNMT_TEMT)). Polypeptide-related sequences of the invention can also possess or interact with C1q domains, which are protein domains involved in activating the serum complement system (<http://pfam.wustl.edu/cgi-bin/getdesc?name=C1q>). Polypeptide-related sequences of the invention can also possess or interact with collagen triple helix repeat (Collagen) domains, which are protein domains that typically form extracellular connective tissue (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Collagen>).

[0196] Polypeptide-related sequences of the invention can also possess or interact with the hyaluronan/mRNA binding family (HABP4\_PAIRBP1) domain, which is a protein domain that can bind to the glucosaminoglycan hyaluronan, and to RNA ([http://pfam.wustl.edu/cgi-bin/getdesc?name=HABP4\\_PAIRBP1](http://pfam.wustl.edu/cgi-bin/getdesc?name=HABP4_PAIRBP1)). Polypeptide-related sequences of the invention can also possess or interact with eucaryotic aspartyl protease (asp) domains, which are protein domains that cleave peptide bonds; proteins with this domain include pepsins, cathepsins, and rennin (<http://pfam.wustl.edu/cgi-bin/getdesc?name=asp>). Polypeptide-related sequences of the invention can also possess or interact with trypsin domains, which are protein domains that function as serine proteases (<http://pfam.wustl.edu/cgi-bin/getdesc?name=trypsin>). Polypeptide-related sequences of the invention can also possess or interact with Kunitz/Bovine pancreatic trypsin inhibitor (Kunitz\_BPTI) domains, which are protein domains that is found in serine protease inhibitors ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Kunitz\\_BPTI](http://pfam.wustl.edu/cgi-bin/getdesc?name=Kunitz_BPTI)). Polypeptide-related sequences of the invention can also possess or interact with proliferating cell nuclear antigen, N-terminal (PCNA) domains, which are protein domains that are found on non-histone acidic nuclear proteins, and play a role in controlling DNA replication (<http://pfam.wustl.edu/cgi-bin/getdesc?name=PCNA>).

#### **Oxygenase-Related Sequences**

[0197] Oxygenases are enzymes that catalyze the incorporation of molecular oxygen into organic substances. Dioxygenases, also known as oxygen transferases, catalyze the introduction of both atoms of molecular oxygen, and typically contain iron. Monooxygenases, also known as mixed function oxygenases, introduce one oxygen atom; the other is reduced to water. Examples of oxygenase-related sequences include cytochrome oxygenases, heme oxygenases, cyclooxygenases, lipoxygenases, and peptide-aspartate beta-dioxygenase.

[0198] Oxygenase-related sequences can possess or interact with alkyl hydroperoxide reductase/thiol specific antioxidant (AhpC-TSA) domains, which are responsible for providing a defense against sulfur-containing radicals; proteins that possess this domain include allergens, e.g., asp f3, mal f2, and mal f3 (<http://pfam.wustl.edu/cgi-bin/getdesc?name=AhpC-TSA>). Oxygenase-related sequences can also possess or interact with monooxygenase domains, which are protein domains that utilize flavin adenine dinucleotide (FAD) (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Monooxygenase>). Oxygenase-related sequences can also possess or interact with dioxygenase domains, which are protein domains that catalyze the incorporation of both atoms of molecular oxygen into substrates (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Dioxygenase>).

#### **Peroxidase-Related Sequences**

[0199] Peroxidases are enzymes that catalyze the reduction of hydrogen peroxide. Peroxidases are generally located within peroxisomes, which are intracellular organelles that metabolize fatty acids and toxic compounds. Disorders associated with peroxidase-related sequences include X-linked adrenoleukodystrophy. Examples of peroxidase-related sequences include glutathione peroxidases, thiol peroxidases, catalases, horseradish peroxidases, anionic peroxidases, and thyroid peroxidases.

[0200] Peroxidase-related sequences can possess or interact with alkyl hydroperoxide reductase/thiol specific antioxidant (AhpC-TSA) domains, which are protein domains that can reduce organic hydroperoxides (<http://pfam.wustl.edu/cgi-bin/getdesc?name=AhpC-TSA>).

#### **Phospholipase-Related Sequences**

[0201] Phospholipases are enzymes that act on phospholipids. They characteristically generate products that are active in signal transduction pathways. For example, phospholipase C hydrolyzes phosphatidylinositol biphosphate (PIP<sub>2</sub>) to generate the two intracellular mediators, inositol triphosphate (IP<sub>3</sub>) and diacylglycerol. IP<sub>3</sub> releases Ca<sup>2+</sup> from stores in the endoplasmic reticulum, increasing the cytosolic Ca<sup>2+</sup> concentration. Diacylglycerol remains in the plasma membrane and activates protein kinase C.

[0202] Phospholipase activity is involved in the synthesis of eicosanoids, inflammatory mediators that include prostaglandins, prostacyclins, thromboxanes, and leukotrienes. Corticosteroid hormones, such as cortisone, for example, inhibit

phospholipase activity in the first step of the eicosanoid synthesis pathway. Corticosteroid hormones are widely used clinically to treat noninfectious inflammatory diseases, such as some forms of arthritis (Ribardo et al., 2002).

[0203] Phospholipids play a pivotal role in the modulation of intestinal inflammation. The mucosal surface of the digestive tract functions as a regulatory barrier between the gastrointestinal lumen and the underlying mucosal immune system. Phospholipids help preserve the mucosa following various forms of injury or physiological damage to the lumen, thus preventing invasion of harmful luminal factors into the host, which subsequently may lead to inflammation, or a pathological immune response, both promoting and inhibiting gastrointestinal inflammation and immunity (Sturm and Dignass, 2002).

[0204] Phospholipase-related sequences can possess or interact with lysophospholipase catalytic (PLA2\_B) domains, which catalyze the release of fatty acids from lysophospholipids ([http://pfam.wustl.edu/cgi-bin/getdesc?name=PLA2\\_B](http://pfam.wustl.edu/cgi-bin/getdesc?name=PLA2_B)). Phospholipase-related sequences can also possess or interact with phospholipase/carboxylesterase (abhydrolase\_2) domains, which have broad substrate specificity ([http://pfam.wustl.edu/cgi-bin/getdesc?name=abhydrolase\\_2](http://pfam.wustl.edu/cgi-bin/getdesc?name=abhydrolase_2)). Phospholipase-related sequences can also possess or interact with GDSL-like lipase/acylhydrolase (Lipase\_GDSL) domains, which are present in lipolytic enzymes with serine in the active site ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Lipase\\_GDSL](http://pfam.wustl.edu/cgi-bin/getdesc?name=Lipase_GDSL)).

#### **Prosaposin-Related Sequences**

[0205] Saposins are small lysosomal proteins that activate lysosomal lipid-degrading enzymes, including enzymes that metabolize sphingosine. They typically isolate lipids from their membrane surroundings, and increase their accessibility to degradative enzymes. Mammalian saposins are synthesized as a single precursor molecule, prosaposin, which becomes an active saposin following proteolytic activation. Examples of prosaposin-related sequences include saposin A, saposin B, and saposin C. Disorders associated with prosaposin-related sequences include neurodegenerative diseases similar to Tay-Sachs and Sandhoff diseases, e.g., Gaucher's disease, which is described above.

[0206] Prosaposin-related sequences can possess or interact with saposin-A (SAPA) domains, saposin B1 (SapB\_1) domains, and saposin B2 (SapB\_2) domains, which are described above.



### Proteasome-Related Sequences

[0207] Proteasomes are intracellular complexes that degrade proteins.

Proteasomes recognize proteins that have been marked for destruction by the addition of an ubiquitin molecule, unfold these ubiquitinated proteins, cleave them into small peptides of 6-12 amino acids, and release them into the cytosol (Mitch and Goldberg, 1996). Examples of proteasome-related sequences include 26S proteasome subunits, 26S proteasome regulatory chains, and ubiquitin.

[0208] Proteasome-related sequences can possess or interact with proteasome/cyclosome repeat (PC\_rep) domains, which are protein domains that are present in regulatory subunits of the proteasome ([http://pfam.wustl.edu/cgi-bin/getdesc?name=PC\\_rep](http://pfam.wustl.edu/cgi-bin/getdesc?name=PC_rep)). Proteasome-related sequences can also possess or interact with Mov34/MPN/PAD-1 family (Mov34) domains, which are protein domains found at the N-terminus of regulatory subunits of the proteasome (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Mov34>).

### Reductase-Related Sequences

[0209] Reductases are enzymes that catalyze reduction reactions, i.e., reactions in which hydrogen is combined with a molecule, or reactions in which oxygen is removed from a molecule. Examples of reductases include dehydrogenase reductases, oxidoreductases, quinone reductases, CoA reductases, dihydrofolate reductases, tetrahydrofolate reductases, carbonyl reductases, nitrate reductases, epoxide reductases, NADP(+) reductases, ribonucleotide reductases, and thioredoxin reductases (Loeffen et al., 1998).

[0210] Reductase-related sequences can possess or interact with short chain dehydrogenase (adh\_short) domains, which are present in a wide variety of proteins ([http://pfam.wustl.edu/cgi-bin/getdesc?name=adh\\_short](http://pfam.wustl.edu/cgi-bin/getdesc?name=adh_short)). Reductase-related sequences can possess or interact with NADH-Ubiquinone oxidoreductase (complex I), chain 5 N-terminus (oxidored\_q1\_N) domains, which are protein domains that catalyze the transfer of electrons from NADH to ubiquinone in a reaction that can be associated with proton translocation across a membrane ([http://pfam.wustl.edu/cgi-bin/getdesc?name=oxidored\\_q1\\_N](http://pfam.wustl.edu/cgi-bin/getdesc?name=oxidored_q1_N)).

### Reverse Transcriptase-Related Sequences

[0211] Reverse transcriptases are enzymes that make double stranded DNA copies from single stranded nucleic acid template molecules. Typically, a reverse transcriptase is a DNA polymerase that can copy both RNA and DNA

templates, and has an integral RNase H activity (Lim et al., 2002). The two enzymatic domains of reverse transcriptase reflect these two activities; the first is a DNA polymerase domain that can use either RNA or DNA as a template to synthesize either the minus-strand or the plus strand of DNA, and the second is an RNase H domain that degrades the RNA in RNA-DNA hybrids (Coffin, 1997; Wu and Gallo, 1975).

[0212] Reverse transcriptase plays a role in the replication of some viruses, e.g., retroviruses. It copies the retroviral RNA genome to produce a single minus strand of DNA, then catalyzes the synthesis of a complementary plus strand. Accordingly, reverse transcriptase is a therapeutic target for conditions that involve retroviruses, e.g., Acquired Immune Deficiency Syndrome (AIDS). A number of anti-retroviral drugs inhibit reverse transcriptase (Frank, 2002).

[0213] Reverse transcriptase is also a standard scientific research tool in the field of molecular biology. The reverse transcriptase polymerase chain reaction (RT-PCR) amplifies specific DNA sequences rapidly, and *in vitro*. RT-PCR can detect trace amounts of RNA and DNA, and is used in a wide range of applications, including forensics, the diagnosis of genetic diseases, determination of the prognosis of diagnosed diseases, and the detection of viral infection (Alberts, et al., 1994). For example, reverse transcriptase is used to diagnose cancer (Rowland, 2002), and to provide prognostic information about the predicted survival of patients with prostate cancer (Kantoff et al., 2001).

[0214] An example of a reverse transcriptase is telomerase, a general tumor marker with a reverse transcriptase catalytic subunit (Kirkpatrick and Mokbel, 2001). Most human somatic cells do not express the telomerase reverse transcriptase gene; conversely, most cancer cells express this gene (Ducrest et al., 2002; Kyo et al., 2000). The human telomerase reverse transcriptase promoter has been placed in gene therapy vectors that specifically target telomerase-positive tumor cells, and spare nearby telomerase-negative cells (Pan and Koenenman, 1999). Human telomerase reverse transcriptase is also recognized as a tumor antigen that can be a target for immunotherapeutic approaches to cancer (Gordan and Vonderheide, 2002).

[0215] Reverse transcriptase-related sequences can possess or interact with rvt, transposase\_22, WD40, and Exo\_endo\_phos domains, all of which are described above.

### **Ribosome-Related Sequences**

[0216] A ribosome is a particle comprised of ribosomal proteins and ribosomal RNA that catalyzes protein synthesis from messenger RNA. Ribosomes are composed of two subunits, the large (L) subunit and the small (S) subunit. The typical mammalian ribosome comprises four RNA molecules and approximately eighty different proteins, which are highly conserved among prokaryotes and eukaryotes, and perform a variety of tasks related to protein synthesis . e.g., coordinating protein synthesis in a manner that maintains cell homeostasis (Yoshihama et al., 2002; Kenmochi et al., 1998).

[0217] Ribosomal proteins can perform functions independent of their involvement in protein synthesis. For example, they are involved in cell-cycle progression, e.g., as cell cycle checkpoints, and mediators of homologous recombination, embryogenesis, and skeletal development (Yoshihama et al., 2002; Chen and Ioannou, 1999). They also contribute to the regulation of cell growth, transformation, and death, and can induce apoptosis (Chen and Ioannou, 1999; Naora et al., 1999). Mutations in ribosomal proteins are associated with human diseases, including Down syndrome, Diamond-Blackfan anemia, Turner syndrome, and Noonan syndrome (Yoshihama et al., 2002).

[0218] Ribosomal proteins have been grouped into protein families on the basis of sequence similarities in functional domains. One family of ribosomal proteins, the ribosomal protein L11, RNA binding (Ribosomal\_L11) domain, is comprised of members that possess the L11 RNA binding domain; this family includes the ribosomal proteins L11 and L12, which are components of the large subunit. L11 is a protein of 140 to 165 amino-acids that binds to a 23S RNA molecule, the C-terminal region of which is buried within the ribosomal structure ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_L11](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_L11)). Another family of large ribosomal subunit proteins possess the ribosomal protein L13e (Ribosomal\_L13e) domain, which is found in a wide range of vertebrates and in lower-order species ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_L13e](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_L13e)), as is the ribosomal protein L44 (Ribosomal\_L44) domain ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_L44](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_L44)).

[0219] Additional ribosomal protein families encompass small subunit proteins. The ribosomal protein S6e (Ribosomal\_S6e) domain is present in a family of proteins which includes protein kinase substrates that control cell growth and

proliferation by selectively translating particular classes of mRNA ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_S6e](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_S6e)). The ribosomal protein S8e (Ribosomal\_S8e) domain is present in a family of proteins comprising approximately 220 amino acids in eukaryotes, and about 125 amino acids in archaebacteria ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_S8e](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_S8e)). The ribosomal protein S10p/S20e (Ribosomal\_S10) domain is present in a family of proteins which includes the small ribosomal subunit S10 from prokaryotes and S20 from eukaryotes ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal\\_S10](http://pfam.wustl.edu/cgi-bin/getdesc?name=Ribosomal_S10)). S10 is involved in binding transfer RNA to the ribosome, and also operates as a transcriptional elongation factor.

#### **RNase-Related Sequences**

[0220] RNases are enzymes that cleave RNA. RNases generally recognize their targets by tertiary structure, rather than by sequence; they include exonucleases, which remove the terminal base in an RNA sequence, and endonucleases, which can cleave non-terminal bases. Examples of RNases include RNase E, which is involved in the formation of 5S ribosomal RNA from pre-ribosomal RNA; RNase F, which cleaves both viral and host RNA in response to interferons, inhibiting protein synthesis; RNase H, which is specific for the RNA strand of an RNA-DNA hybrid; RNase P, which generates transfer RNA from precursor transcripts; and RNase T, which removes the terminal AMP from nonaminoacylated tRNA (Coffin, et al., 1997).

[0221] RNase-related sequences can possess or interact with rvt, rve, RNase H, and gag\_p30 domains, all of which are described above.

#### **RNase H-Related Sequences**

[0222] RNase H is a nuclease specific for the RNA strand of an RNA-DNA hybrid that cleaves phosphodiester bonds to produce molecules with 3'-OH and 5'-PO<sub>4</sub> ends. Multiple forms of RNase H are present in both prokaryotes and eukaryotes. RNase H may be part of larger polypeptides and its activity can be influenced by other regions of these polypeptides (Coffin, et al., 1997; Crouch 1990).

[0223] During retroviral replication, RNase H activity forms oligonucleotides that prime DNA synthesis. Therefore, the RNase H activity of reverse transcriptase is a target for therapeutic intervention. For example, small molecule inhibitors of retroviral RNase H function have shown promise in managing HIV infection (Klarman, et al., 2002).

[0224] Another therapeutic indication for RNase H is the regulation of cancer genes by targeting mRNA translation. Antisense deoxyoligonucleotides down-regulate mRNA expression by annealing to specific regions of an mRNA. Formation of the DNA:RNA heteroduplex then triggers mRNA cleavage by RNase H. Cleavage is rapidly followed by further degradation, irreversibly preventing translation of the target mRNA. Antisense deoxyoligonucleotides that trigger RNase H activity can thus be used as cancer therapeutic agents (Crooke, 1996; Curcio et al., 1997).

[0225] RNase H-related sequences can possess or interact with maseH, Gag\_p30, rvt, and rve domains, all of which are described above.

### **SH3-Related Sequences**

[0226] Src homology region 3 (SH3) is a polypeptide domain commonly found in intracellular signaling proteins; it binds with moderate affinity and selectivity to proline-rich ligands. SH3 domains are heterogeneous; different SH3 domains bind to different proline-rich sequences (Gmeiner and Horita, 2001). SH3 domains are involved in a wide variety of biological processes, including mediating the assembly of large multiprotein complexes, regulating enzyme activity, and modulating the local concentration or subcellular localization of signaling pathway components (Mayer, 2001). Examples of SH3-related sequences include phosphotyrosine receptors, membrane associated guanylate kinases, mitogen-activated protein kinases, myosin 1, the Crk adaptor protein, phospholipase C- $\gamma$ , Grb2, Sos, src-SH3, Abl-SH3, the Nck adaptor, and alpha-spectrin-SH3.

[0227] SH3-related sequences can possess or interact with SH3 domains, which are protein domains of approximately 50-70 amino acids, and are present in a large number of proteins involved in intracellular signaling (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SH3>). SH3-related sequences can also possess or interact with SH3 domain-binding protein 5 (SH3BP5) domains, which are protein domains that act as a substrate for c-Jun N-terminal kinase (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SH3BP5>).

### **Stem Cell-Related Sequences**

[0228] Stem cells are pluripotent or multipotent cells that generate maturing cells in multiple differentiation lineages. Pluripotent cells have the capacity to differentiate into each and every cell present in the organism. Embryonic stem cells are pluripotent; they can differentiate into any of the cells present in the adult.

Multipotent cells have the ability to differentiate into more than one cell type. Organ-specific stem cells are multipotent; they can differentiate into any of the cells of the organ they inhabit.

[0229] When they divide *in vivo*, both pluripotent and multipotent stem cells can maintain their pluripotency or multipotency while giving rise to differentiated progeny. Thus, stem cells can produce replicas of themselves which are pluri- or multipotent, and are also able to differentiate into lineage-restricted committed progenitor cells. For example, hematopoietic stem cells, which are multipotent cells specifically able to form blood cells, can divide to produce replicate hematopoietic stem cells. They can also divide to produce more highly differentiated cells, which are precursors of blood cells. The precursors differentiate, sometimes through several generations of cells, into blood cells. A hematopoietic stem cell can also divide into a cell with the capacity to form, for example, a relatively undifferentiated cell that is committed to differentiate into, i.e., granulocytes, or erythrocytes, or another type of blood cell.

[0230] Stem cells can also reproduce and differentiate *in vitro*. Embryonic stem cells have been directed to differentiate into cardiac muscle cells *in vitro* and, alternatively, into early progenitors of neural stem cells, and then into mature neurons and glial cells *in vitro* (Trounson, 2002).

[0231] Stem cell therapy is effective in treating cancer in humans (Slavin et al., 2001), and offers several advantages over traditional cancer therapies (Weissman, 2000). One advantage of stem cell therapy exists when used in conjunction with radiation therapy. In radiation therapy for cancer, the dose of radiation necessary to kill the cancer cells in an organ can also be sufficient to destroy the healthy cells of the organ. In combined stem cell and radiation therapy, an organ is first treated with sufficient radiation to destroy all of the cancer cells and most or all of the healthy cells, but then stem cells are infused to repopulate the organ. In the ensuing weeks, as the cancer cells and healthy cells die, the stem cells replace the healthy cells. Another advantage of this approach, compared to heterologous organ transplants, is that there is no risk of rejection, since stem cells do not provoke an immune response. A further advantage is that stem cells are inherently programmed to regulate their numbers and differentiation status, i.e., once provided to the patient, the necessary number will differentiate, and the rest will remain undifferentiated (Weissman, 2000).

[0232] Stem cell therapy is also effective in treating autoimmune disease in humans. For example, immunosuppression in conjunction with stem-cell transplantation has induced remission in patients with refractory, severe rheumatic autoimmune disease (Van Laar and Tyndall, 2003). Patients with rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, and juvenile idiopathic arthritis have benefited from stem cell transplants (Van Laar and Tyndall, 2003).

[0233] Preclinical studies also suggest the potential of stem cell transplantation for the treatment of neural and muscular injuries and disorders, including those of the central nervous system, peripheral nervous system, and skeletal, cardiac and smooth muscle (Deasy and Huard, 2002). Stem cells transplanted into the bone marrow of mice migrate to the site of injured muscle and differentiate into new muscle cells. For example, patients with myasthenia gravis, muscular dystrophies, amyotrophic lateral sclerosis, congestive heart failure, Parkinson's disease, and Alzheimer's disease may benefit from stem cell therapy (Henningson, 2003).

[0234] In addition to therapeutic uses, research using stem cells can provide useful information about normal stem cell function and the pathogenesis of disease. Stem cells derived from a patient with a genetic disease can provide a tool for studying that disease. To derive these stem cells, a somatic cell, i.e., a cell that is not in the oocyte or spermatocyte lineage, is donated by the patient, and the nucleus is removed and transferred to an unfertilized human oocyte. This nuclear transplant procedure produces, at the blastocyst stage of development, embryonic stem cells with the same set of genes as the patient with the genetic disease. Studying these cells, and their progeny in vitro, permits analysis of a specific model of the disease. For example, placing stem cells derived from a patient with a genetic disorder under the control of various stem cell regulatory factors can elicit abnormal responses from the affected stem cells compared to stem cells derived from a healthy individual's somatic nucleus.

[0235] Embryonic stem cell-related sequences can possess or interact with the stem cell factor (SCF) domain, a transmembrane domain having a soluble, secreted form, which is involved in hematopoiesis, and which binds to and activates a receptor tyrosine kinase, stimulating the proliferation of mast cells and augmenting the proliferation of myeloid and lymphoid hematopoietic progenitors in bone marrow culture (<http://pfam.wustl.edu/cgi-bin/getdesc?name=SCF>).

[0236] Certain stem cell related sequences can possess the ability to maintain the stem cell in undifferentiated state while allowing cell proliferation. Such compositions can be useful in *ex vivo* cell therapy to expand populations of cells for cell replacement therapy.

[0237] Certain stem cell related sequences can possess the ability to cause cell differentiation to a relatively mature cell type and are useful to *in vivo* or *ex vivo* therapy to compensate for deficiency of such relatively mature cell type.

#### **Synthetase-Related Sequences**

[0238] A synthetase is an enzyme that catalyzes the synthesis of a molecule. Synthetases comprise a broad class of enzymes; they catalyze the synthesis of nucleic acids, peptides, and lipids (Agou et al., 1996). Examples of synthetases include lysyl-tRNA synthetase, asparaginyl t-RNA synthetase, holocarboxylase synthetase, carbamyl phosphate synthetase I, and argininosuccinate synthetase.

[0239] Synthetase-related sequences can possess or interact with transfer RNA synthetase domains, which are protein domains that activate amino acids and transfer them to specific transfer RNA molecules as a step in protein biosynthesis ([http://pfam.wustl.edu/cgi-bin/getdesc?name=tRNA-synt\\_2](http://pfam.wustl.edu/cgi-bin/getdesc?name=tRNA-synt_2)). The 20 aminoacyl-tRNA synthetases are divided into class I and class II, each of which contain multiple synthetases with different specificities. For example, there is a protein domain involved in the asparagines, aspartic acid, and lysine synthesis ([http://pfam.wustl.edu/cgi-bin/textsearch?terms=tRNA-synt&search\\_what=all&sections=DE&sections=CC&size=100](http://pfam.wustl.edu/cgi-bin/textsearch?terms=tRNA-synt&search_what=all&sections=DE&sections=CC&size=100)). Synthetase-related sequences can also possess or interact with lipid-A-disaccharide synthetase (LpxB) domains, which are protein domains that catalyze the synthesis of disaccharides (<http://pfam.wustl.edu/cgi-bin/getdesc?name=LpxB>).

#### **TATA Box-Related Sequences**

[0240] A TATA box is a consensus sequence in the promoter region of many eucaryotic genes that binds a general transcription factor and plays a role in specifying the position for transcription initiation. TATA boxes are generally found approximately 25 nucleotides before the site of transcription initiation (Chalut et al., 1995). Examples of TATA box-related sequences include TATA box binding protein, 13 TATA/TBP, and small nuclear RNA-activating protein 190 Myb DNA.

[0241] TATA box-related sequences can possess or interact with transcription factor TFIID, also known as the TATA-binding protein (TBP) domain,



which is a protein domain that specifically binds to the TATA box promoter element (<http://pfam.wustl.edu/cgi-bin/getdesc?name=TBP>). TATA box-related sequences can also possess or interact with HMG14 and HMG17 (HMG14\_17) domains, which are members of a family of high mobility group proteins, described above ([http://pfam.wustl.edu/cgi-bin/getdesc?name=HMG14\\_17](http://pfam.wustl.edu/cgi-bin/getdesc?name=HMG14_17)).

#### **Tat-Related Sequences**

[0242] Tat is a human immunodeficiency virus (HIV) protein involved in viral production of new RNA genomes and new complete viral particles. Tat is also involved in AIDS pathogenesis; it plays a role in reactivating latent viruses, e.g., the JC retrovirus; it is involved in the development of AIDS-related Kaposi's Sarcoma; and it depresses the function of, and induces apoptosis in, helper CD4 cells (Yu et al., 1995). Examples of Tat-related sequences include Tat-associated proteins, e.g., Tap, HIV-1 Rev, and tat-associated kinase (also known as positive transcriptional elongation factor b).

[0243] Tat-related sequences can possess or interact with transactivating regulatory protein (Tat) domains, which are protein domains that contribute to efficient transcription of a viral genome (<http://pfam.wustl.edu/cgi-bin/getdesc?name=Tat>). Tat-related sequences can also possess or interact with mitochondrial glycoprotein (MAM33) domains, which are protein domains found in mitochondrial matrix proteins, and which can be involved in mitochondrial oxidative phosphorylation and in interactions between the nucleus and the mitochondria (<http://pfam.wustl.edu/cgi-bin/getdesc?name=MAM33>).

#### **Transferase-Related Sequences**

[0244] Transferases are enzymes that transfer a designated group of atoms from a donor molecule to an acceptor molecule. For example, acyl transferases transfer acyl groups, methyl transferases transfer methyl groups, nucleotidyl transferases transfer nucleotides, prenyltransferases transfer prenyl groups, and glycosyl transferases transfer glycosyl groups (Lin et al., 1996). Examples of transferases include acetyltransferases, hydroxymethyltransferases, sialyltransferases, arginine N-methyltransferase, glucuronosyltransferase, NTP-transferase, and GDP-mannose pyrophosphorylase B.

[0245] Transferase-related sequences possess or interact with UDP-glucuronosyl and UDP-glycosyl transferase domains, which are protein domains found in a superfamily of enzymes that catalyze the addition of the glycosyl group

from a UTP-sugar to a small hydrophobic molecule (<http://pfam.wustl.edu/cgi-bin/getdesc?name=UDPGT>). Transferase-related sequences also possess or interact with nucleotide transferase (NTP\_transferase) domains, which are protein domains that transfer nucleotides onto phosphorylated sugars ([http://pfam.wustl.edu/cgi-bin/getdesc?name=NTP\\_transferase](http://pfam.wustl.edu/cgi-bin/getdesc?name=NTP_transferase)).

### Transposase-Related Sequences

[0246] Transposases are site-specific recombination enzymes that catalyze the transposition of a segment of DNA from one part of the genome to another. The movable segments are called transposable elements; each transposable element is occasionally moved by a transposase, which functions as an integrase, by inserting DNA sequences into other DNA sequences. Transposases are often encoded by the DNA of the transposable element itself. Transposases bind specifically to terminal inverted repeats of 10-500 bp that are characteristically part of transposable elements (Smit and Riggs, 1996). They catalyze both cutting and pasting of a transposable element from one segment of the genome to another. Sequences related to transposases can have other functions, e.g., as transcription factors, or in the assembly of centromere proteins (Smit and Riggs, 1996). Examples of transposase-related sequences include mariner, pogo, hobo, tigger, MER37, Galileo, Occan, Impala, Tn MER11, MsqTc3, and the sleeping beauty transposon system (Robertson and Zuppano, 1997; Robertson, 1996; Smit and Riggs, 1996).

[0247] Transposase-related sequences can possess or interact with a transposase 1 (Transposase\_1) domain, which is characterized by sequences that can excise and/or insert mobile genetic elements such as transposons or insertion sequences; for example, mariner possesses a transposase 1 domain ([http://pfam.wustl.edu/cgi-bin/getdesc?name=Transposase\\_1](http://pfam.wustl.edu/cgi-bin/getdesc?name=Transposase_1)). Transposase-related sequences can also possess or interact with L1 transposable element (Transposase\_22) domains, which have been described above. Transposase-related sequences can also possess or interact with a DDE endonuclease (DDE) domain, which is responsible for coordinating metal ions needed for endonuclease catalytic activity (<http://pfam.wustl.edu/cgi-bin/getdesc?name=DDE>). Transposase-related sequences can additionally possess or interact with a zinc finger, C2H2 type (zf-C2H2) domain, which bind nucleic acids using a mechanism that involves coordinating a zinc atom with a pair of cysteine residues and a pair of histidine residues (<http://pfam.wustl.edu/cgi-bin/getdesc?name=zf-C2H2>). Transposase-related sequences can also possess or

interact with a reverse transcriptase (rtv) domain, and/or a low-density lipoprotein receptor (ldl\_rece) domain, both of which are described above.

#### Ubiquitin-Related Sequences

[0248] Ubiquitin is a protein found in all eucaryotic cells examined to date. When it is linked to the lysine side chain of a protein by the formation of an amide bond with its C-terminal glycine, ubiquitin renders the ubiquitin-bound protein subject to rapid proteolysis in the proteasome. In addition to its role in the selective degradation of cellular proteins, ubiquitin also plays a role in maintaining chromosome structure, regulating gene expression, responding to stresses on the organism, the regulation of gene expression, and ribosome biogenesis. Examples of ubiquitin-related sequences include elongins, ubiquitin-specific proteases, ubiquitin-calmodulin ligase, ubiquitin carrier protein kinase, ubiquitin N-alpha-protein hydrolase, and the small ubiquitin-related modifier (Sumo-1) (Kamitani et al., 1997).

[0249] Ubiquitin-related sequences can possess or interact with a ubiquitin domain, which is a conserved sequence of approximately 76 amino acid residues that comprise the protein ubiquitin (<http://pfam.wustl.edu/cgi-bin/getdesc?name=ubiquitin>). Ubiquitin-related sequences can also possess or interact a ubiquitin carboxyl-terminal hydrolase (UCH) domain, which is a protein domain that comprises a thiol protease that recognizes and hydrolyses the peptide bond at the C-terminal glycine of ubiquitin (<http://pfam.wustl.edu/cgi-bin/getdesc?name=UCH>).

#### Virus-Related Sequences

[0250] The human chromosome has integrated endogenous genes that are related to viral genes. Some endogenous viral genes, e.g., the retroviral HERV-W family, are widely and heterogeneously dispersed among human chromosomes (Voisset et al., 2000; Everett et al., 1997; Werner et al., 1990). Endogenous proviruses are usually transcriptionally silent, but are expressed under certain conditions (Coffin et al., 1997). Endogenous viral expression can be specific to host factors, such as cell type or stage of differentiation, as well as other factors including the position on the chromosome, the influence of *cis*-acting sequences, or the presence of host-mediated DNA methylation (Coffin).

[0251] Endogenous viral expression can have a number of consequences, both beneficial and detrimental. Among the beneficial consequences is the ability of endogenous retroviruses to confer resistance to infection by exogenous

viruses. For example, mice with endogenous mouse mammary tumor virus (MMTV) can be immune to exogenous infection (Golovkina, et al., 1992). Among the detrimental effects is a causative role in disease. Evidence indicates an association between endogenous viruses with cancers and autoimmune diseases (Coffin et al., 1997). For example, spontaneous tumors of specific origin, murine mammary adenocarcinomas, and murine T-cell lymphomas have been associated with the presence of specific endogenous retroviruses. Furthermore, a transformed phenotype is associated with the increased transcription of certain classes of endogenous viral elements (Coffin et al., 1997). With respect to autoimmune disease, an endogenous virus that influences the immunoregulatory process has been associated with spontaneous autoimmune thyroiditis in a chicken model of human Hashimoto disease (Wick et al., 1987). Examples of viral-related proteins include hepatitis B virus x-interacting protein, herpesvirus associated ubiquitin-specific protease, and Coxsackievirus and adenovirus receptor precursor.

[0252] Viral-related sequences can possess or interact with rvt, rve, and gag\_p30 sequences, all of which are described above.

#### **Zinc Finger-Related Sequences**

[0253] A zinc finger domain is a small, self-folding, structural motif of 25 to 30 amino-acid residues present in many nucleic acid-binding proteins. It is comprised of a polypeptide loop held in a hairpin bend and bound to a zinc atom, and includes two conserved cysteine and two conserved histidine residues. Many classes of zinc fingers have been characterized according to the number and positions of the conserved histidine and cysteine residues. The amino acid configuration that holds the zinc atom in a tetrahedral array has a finger-like projection that interacts with nucleotides in the major groove of the bound nucleic acid. Zinc finger motifs have conserved regions near the zinc molecule, and variable regions at the nucleic acid binding site that provide specificity for the nucleic acid sequences they bind. Zinc finger proteins have a variety of functions, including as transcription regulators and intracellular receptors. Zinc finger domains are also involved in protein-protein interactions, e.g., those involving protein kinase C. Recently, zinc finger nucleases have been used to target genes for gene replacement by homologous recombination (Bibikova et al., 2003). Examples of zinc finger proteins include XC3H-3b, the transcription factor Slug, and transcription factor IIIA.

[0254] Zinc finger-related sequences can possess or interact with a zinc finger C2H2 type (zf-C2H2) domain, which binds a zinc atom with two cysteine and two histidine residues, and is utilized, e.g., in RNA transcription (<http://pfam.wustl.edu/cgi-bin/getdesc?name=zf-C2H2>). Zinc finger-related sequences can also possess or interact with a C3HC4 type, RING finger (zf-C3HC4) domain, which is a specialized type of zinc finger domain comprised of 40 to 60 amino acids that binds two zinc atoms; variants of RING-finger domains include the C3HC4-type and the C3H2C3-type (<http://pfam.wustl.edu/cgi-bin/getdesc?name=zf-C3HC4>). Proteins with RING-finger domains have developmental and functional roles; they are involved in intracellular receptor binding, and in mediating protein-protein interactions (Gray et al., 2000). RING-finger domains can exhibit ubiquitin-protein ligase activity, and can bind to E2 ubiquitin-conjugating enzymes.

[0255] Zinc finger-related sequences can also possess or interact with a zinc knuckle (zf-CCHC) domain, which is an 18-amino acid zinc finger domain found in RNA-binding and single strand DNA-binding proteins; they are often involved in eukaryotic gene regulation (<http://pfam.wustl.edu/cgi-bin/getdesc?name=zf-CCHC>). Zinc knuckles are also found in retroviral gag and nucleocapsid proteins, where they function in genome packaging, and early in the infection process. Zinc finger-related sequences can also possess or interact with a BTB/POZ (BTB) domain, which mediates both homomeric and heteromeric protein dimerization (<http://pfam.wustl.edu/cgi-bin/getdesc?name=BTB>). Zinc finger-related sequences can also possess or interact with NF-X1 type zinc finger (zf-NF-X1) domains, which are found in the transcriptional repressor NK-X1, where they repress transcription of HLA-DRA, and in the shuttle craft protein, which plays a role in late stage embryonic neurogenesis (<http://pfam.wustl.edu/cgi-bin/getdesc?name=zf-NF-X1>). Zinc finger-related sequences can also possess or interact with a KRAB box (KRAB) domain, also known as a Kruppel-associated box, which is comprised of approximately 75 amino acids, enriched in charged amino acids, and involved in protein-protein interactions (<http://pfam.wustl.edu/cgi-bin/getdesc?name=KRAB>). KRAB domains can function as transcription factors, e.g., as a transcriptional repressor, and can assume roles in cell differentiation and development (Aubry et al., 1992; Lovering and Trowsdale, 1991). Zinc finger-related sequences can possess or interact with a transposase\_22 domain, which is described above.

# **INDUSTRIAL APPLICABILITY**

[0256] The invention provides sequences related to secreted sequences, single-transmembrane sequences, multiple-transmembrane sequences, kinase-related sequences, ligase-related sequences, nuclear hormone receptor-related sequences, phosphatase-related sequences, protease-related sequences, phosphodiesterase-related sequences, kinesin-related sequences, immunoglobulin-related sequences, T-cell receptor-related sequences, glycosylphosphatidylinositol anchor-related sequences, and sequences related to other nucleic acid and amino acid sequences of the invention, including activators, adaptors, adhesion molecules, ATPases, ATP, breakpoints, channels, checkpoints, complexes, dehydrogenases, disintegrins, endopeptidases, germ-cells, GTPases, helicases, hydrolases, integrases, integrins, isomerases, membranes, mucins, oxygenases, peroxidases, phospholipases, prosaposins, proteosomes, reductases, reverse transcriptases, RNases, RNases H, SH3, synthetases, TATA boxes, Tat proteins, transferases, transposases, ubiquitins, and viruses. The invention provides for novel polynucleotides, related novel polypeptides and active fragments thereof, as well as novel nucleic acid compositions encoding these polypeptides, compositions comprising the related polypeptides, and methods for their use.

[0257] The present invention also provides for vectors, host cells, and methods for producing the polynucleotides and polypeptides of the invention in these vectors and host cells. The present invention further provides for antisense molecules that are capable of regulating the expression of the polynucleotides or polypeptides herein. In addition, modulators, including antibodies that bind specifically to the polypeptides or modulate the activity of the polypeptides, are also provided.

[0258] The present polynucleotides, polypeptides, and modulators find use in therapeutic agent screening/discovery applications, such as screening for receptors or competitive ligands, for use, for example, as small molecule therapeutic drugs. Also provided are methods of modulating a biological activity of a polypeptide and methods of treating associated disease conditions, particularly by administering modulators of the present polypeptides, such as small molecule modulators, antisense molecules, and specific antibodies.

[0259] The present polypeptides, polynucleotides, and modulators find use in a number of diagnostic, prophylactic, and therapeutic applications. The polynucleotides and polypeptides of the invention can be detected by methods

provided herein; these methods are useful in diagnosis, and can be accomplished by the use of diagnostic kits. The polynucleotides and polypeptides of the invention are useful for treating a variety of disorders, including cancer, proliferative disorders, inflammatory disorders, immune disorders, viral disorders, bacterial disorders, and metabolic disorders. For example, subjects who suffer from a deficiency, or a lack of a particular protein, or are otherwise in need of such protein to repair or enhance a desirable function, benefit from the administration of a protein or an active fragment thereof by any conventional routes of administration. These include therapeutic vaccines in the form of nucleic acid or polypeptide vaccines, such as cancer vaccines, where the vaccines can be administered alone, such as naked DNA, or can be facilitated, such as via viral vectors, microsomes, or liposomes. Therapeutic antibodies include those that are administered alone or in combination with cytotoxic agents, such as radioactive or chemotherapeutic agents.

[0260] In particular, the polypeptides, polynucleotides, and modulators of the present invention can be used to treat cancers, including, but not limited to, cancers of the prostate, breast, bone, soft tissue, liver, kidney, ovary, cervix, skin, pancreas, and brain, as well as leukemias, lymphomas, lung cancers such as adenocarcinomas and squamous cell carcinoma, and cancers of gastrointestinal organs such as stomach, colon, and rectum. Further, the polypeptides, polynucleotides, and modulators of the present invention can be used to treat inflammatory, immune, viral, bacterial, and metabolic diseases, disorders, syndromes, or conditions, including, but not limited to, intestinal inflammation and immunity, autoimmune thyroiditis, and retroviral infections, as well as tissue and/or organ hypertrophy.

#### DISCLOSURE OF THE INVENTION

[0261] The present invention features an isolated polynucleotide that encodes a polypeptide. In some embodiments, the polypeptide has at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or at least about 99% amino acid sequence identity with an amino acid sequence derived from a polynucleotide sequence chosen from at least one nucleotide sequence according to SEQ ID NOS.: 1-104. In some embodiments, the polypeptide has an amino acid sequence chosen from at least one amino acid sequence encoded by SEQ ID NOS.: 1-104. In many

embodiments, the polypeptide has at least one activity associated with the naturally occurring encoded polypeptide.

[0262] In some embodiments, the polypeptide includes a signal peptide. In alternative embodiments, the polypeptide comprises a mature form of a protein, from which the signal peptide has been cleaved. In other embodiments, the polypeptide is a signal peptide. In a further aspect, the invention provides fragments of a polypeptide chosen from at least one amino acid sequence encoded by SEQ ID NO.: 1 - 104, where each fragment is an extracellular fragment of the polypeptide, or an extracellular fragment of the polypeptide minus the signal peptide. The invention provides an N-terminal fragment containing a Pfam domain, and a C-terminal fragment containing a Pfam domain and either or both may be biologically active.

[0263] In yet other embodiments, the polypeptides function as secreted proteins. In yet further embodiments, the polypeptides function as single-transmembrane proteins. In yet further embodiments, the polypeptides function as multiple-transmembrane proteins. In yet further embodiments, the polypeptides function as kinases. In yet further embodiments, the polypeptides function as protein kinases. In yet further embodiments, the polypeptides function as ligases. In yet further embodiments, the polypeptides function as nuclear hormone receptors. In yet further embodiments, the polypeptides function as phosphatases. In yet further embodiments, the polypeptides function as proteases. In yet further embodiments, the polypeptides function as phosphodiesterases. In yet further embodiments, the polypeptides function as kinesins. In yet further embodiments, the polypeptides function as immunoglobulins. In yet further embodiments, the polypeptides function as T-cell receptors. In yet further embodiments, the polypeptides function as glycosylphosphatidylinositol anchors.

[0264] In yet further embodiments, the polypeptides function as cytokines. In still further embodiments, the polypeptides function as immune cells. In further embodiments, the polypeptides function as antigens. In yet further embodiments, the polypeptides function as receptors. In other embodiments, the polypeptides function as binding proteins. In other embodiments, the polypeptides function as factors. In further embodiments, the polypeptides function as growth factors. In further embodiments, the polypeptides function as heat-shock proteins. In some embodiments, the polypeptides function as membrane transport proteins. In yet further embodiments, the polypeptides function as ribosomal proteins. In some



embodiments, the polypeptides function as zinc fingers. In some embodiments, the polypeptides function as embryonic stem cell-related peptides. In still further embodiments, the polypeptides function in pathological states. In other embodiments, the polypeptides function as one or more of these.

[0265] In yet further embodiments, the polypeptides function as activators. In yet further embodiments, the polypeptides function as adaptors. In yet further embodiments, the polypeptides function as adhesion molecules. In yet further embodiments, the polypeptides function as ATPases. In yet further embodiments, the polypeptides function as ATP-related polypeptides. In further embodiments, the polypeptides function as channel-related polypeptides. In yet further embodiments, the polypeptides function as checkpoint-related polypeptides. In yet further embodiments, the polypeptides function as complexes. In yet further embodiments, the polypeptides function as dehydrogenases. In yet further embodiments, the polypeptides function as disintegrins. In yet further embodiments, the polypeptides function as endopeptidases. In yet further embodiments, the polypeptides function as germ-cells. In yet further embodiments, the polypeptides function as GTPases. In yet further embodiments, the polypeptides function as helicases. In yet further embodiments, the polypeptides function as hydrolases. In yet further embodiments, the polypeptides function as integrases. In yet further embodiments, the polypeptides function as integrins. In yet further embodiments, the polypeptides function as isomerases. In yet further embodiments, the polypeptides function as membranes. In yet further embodiments, the polypeptides function as mucins. In yet further embodiments, the polypeptides function as oxygenases. In yet further embodiments, the polypeptides function as peroxidases. In some embodiments, the polypeptides function as phospholipases. In yet further embodiments, the polypeptides function as prosaposins. In yet further embodiments, the polypeptides function as proteasomes. In yet further embodiments, the polypeptides function as reductases. In other embodiments, the polypeptides function as reverse transcriptase-related polypeptides. In yet further embodiments, the polypeptides function as RNases. In further embodiments, the polypeptides function as RNase H-related polypeptides. In yet further embodiments, the polypeptides function as SH3-related polypeptides. In yet further embodiments, the polypeptides function as synthetases. In yet further embodiments, the polypeptides function as TATA box-related polypeptides. In yet further embodiments, the polypeptides function as TAT-related polypeptides. In yet

further embodiments, the polypeptides function as transferases. In yet further embodiments, the polypeptides function as transposases. In yet further embodiments, the polypeptides function as ubiquitin-related polypeptides. In yet further embodiments, the polypeptides function as virus-related polypeptides. In other embodiments, the polypeptides function as one or more of these.

[0266] The present invention features an isolated polynucleotide that hybridizes under stringent hybridization conditions to a coding region of at least one nucleotide sequence shown in SEQ ID NOS.: 1 - 104, or a complement thereof.

[0267] The present invention features an isolated polynucleotide that shares at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, at least about 99% nucleotide sequence identity with a nucleotide sequence of the coding region of at least one sequence shown in SEQ ID NOS.: 1 - 104, or a complement thereof. In some embodiments, a subject polynucleotide has the nucleotide sequence shown in at least one of SEQ ID NOS.: 1 - 104, or a coding region thereof.

[0268] The present invention also features a vector, e.g., a recombinant vector, that includes a subject polynucleotide, and a promoter that drives its expression. This vector can transform a host cell, and the present invention further features such host cells, e.g., isolated *in vitro* host cells, and *in vivo* host cells, that comprise a polynucleotide of the invention, or a recombinant vector of the invention.

[0269] The present invention further features a library of polynucleotides, wherein at least one of the polynucleotides comprises the sequence information of a polynucleotide of the invention. In specific embodiments, the library is provided on a nucleic acid array. In some embodiments, the library is provided in computer-readable format.

[0270] The present invention features a pair of isolated nucleic acid molecules, each from about 10 to about 200 nucleotides in length. The first nucleic acid molecule of the pair comprises a sequence of at least 10 contiguous nucleotides having 100% sequence identity to at least one nucleic acid sequence shown in SEQ ID NOS.: 1 - 104. The second nucleic acid molecule of the pair comprises a sequence of at least 10 contiguous nucleotides having 100% sequence identity to the reverse complement of at least one nucleic acid sequence shown in SEQ ID NOS.: 1 - 104. The sequence of said second nucleic acid molecule is located 3' of the nucleic acid sequence of the first nucleic acid molecule shown in SEQ ID NOS.: 1 - 104. The pair

of isolated nucleic acid molecules are useful in a polymerase chain reaction or in any other method known in the art to amplify a nucleic acid that has sequence identity to the sequences shown in SEQ ID NOS.: 1 - 104, particularly when cDNA is used as a template.

[0271] The invention features a method of determining the presence of a polynucleotide substantially identical to a polynucleotide sequence shown in the Sequence Listing, or a complement of such a nucleotide by providing its complement, allowing the polynucleotides to interact, and determining whether such interaction has occurred.

[0272] The invention further features methods of regulating the expression of the subject polynucleotides and encoded polypeptides. The invention provides a method of inhibiting transcription or translation of a first polynucleotide encoding a first polypeptide of the invention by providing a second polynucleotide that hybridizes to the first polynucleotide, and allowing the first polynucleotide to contact and bind to the second polynucleotide. The second polynucleotide can be chosen from an antisense molecule, a ribozyme, and an interfering RNA (RNAi) molecule.

[0273] The present invention further features an isolated polypeptide, e.g., an isolated polypeptide encoded by a polynucleotide, and biologically active fragments of such polypeptide. In some embodiments, the polypeptide is a fusion protein. In some embodiments, the polypeptide has one or more amino acid substitutions, and/or insertions and/or deletions, compared with at least one sequence shown in SEQ ID NOS.: 1 - 104. In some embodiments, the polypeptide has an amino acid sequence derived from at least one nucleotide sequence shown in SEQ ID NOS.: 1 - 104.

[0274] The invention also provides a method of making a polypeptide of the invention by providing a nucleic acid molecule that comprises a polynucleotide sequence encoding a polypeptide of the invention, introducing the nucleic acid molecule into an expression system, and allowing the polypeptide to be produced.

[0275] In some embodiments, the method involves *in vitro* cell-free transcription and/or translation. For example, the expression system can comprise a cell-free expression system, such as an *E. coli* system, a wheat germ extract system, a rabbit reticulocyte system, or a frog oocyte system.

[0276] In certain other embodiments, the expression system can comprise a prokaryotic or eukaryotic cell, for example, a bacterial cell expression system, a fungal cell expression system, such as yeast or *Aspergillus*, a plant cell expression

system, e.g., a cereal plant, a tobacco plant, a tomato plant, or other edible plant, an insect cell expression system, such as SF9 of High Five cells, an amphibian cell expression system, a reptile cell expression system, a crustacean cell expression system, an avian cell expression system, a fish cell expression system, or a mammalian cell expression system, such as one using Chinese Hamster Ovary (CHO) cells. In some embodiments, the method involves culturing a subject host cell under conditions such that the subject polypeptide is produced by the host cells; and recovering the subject polypeptide from the culture, e.g., from within the host cells, or from the culture medium. In further embodiments, the polypeptide can be produced *in vivo* in a multicellular animal or plant, comprising a polynucleotide encoding the subject polypeptide.

[0277] The present invention further features a non-human animal injected with at least one polynucleotide comprising at least one nucleotide sequence chosen from SEQ ID NOS.: 1 - 104, and/or at least one polypeptide comprising at least one amino acid sequence encoded by SEQ ID NOS.: 1 - 104.

[0278] The present invention further features an antibody that specifically recognizes, binds to, interferes with, or modulates the biological activity of a subject polypeptide or a fragment thereof. The polypeptide can be a single-transmembrane protein, multiple-transmembrane protein, kinase, protein kinase, ligase, nuclear hormone receptor, phosphatase, protease, phosphodiesterase, kinesin, immunoglobulin, T-cell receptor, glycosylphosphatidylinositol anchor, or other nucleic acid and amino acid sequences, including, activators, adaptors, adhesion molecules, ATPases, ATP, breakpoints, channels, checkpoints, complexes, dehydrogenases, disintegrins, endopeptidases, germ-cells, GTPases, helicases, hydrolases, integrases, integrins, isomerases, membranes, mucins, oxygenases, peroxidases, phospholipases, prosaposins, proteasomes, reductases, reverse transcriptases, RNases, RNases H, SH3, synthetases, TATA boxes, Tat, transferases, transposases, ubiquitins, and viruses. The fragment can be an extracellular fragment of a subject polypeptide, or an extracellular fragment of a subject polypeptide minus the signal peptide.

[0279] The present invention further features an antibody that specifically inhibits binding of a polypeptide to its ligand or substrate. It also features an antibody that specifically inhibits binding of a polypeptide as a substrate to another molecule.

[0280] Another aspect of the present invention features a library of antibodies or fragments thereof, wherein at least one antibody or fragment thereof specifically binds to at least a portion of a polypeptide comprising an amino acid sequence encoded by SEQ ID NOS.: 1 - 104, and/or wherein at least one antibody or fragment thereof interferes with at least one activity of such polypeptide or fragment thereof. In certain embodiments, the antibody library comprises at least one antibody or fragment thereof that specifically inhibits binding of a subject polypeptide to its ligand or substrate, or that specifically inhibits binding of a subject polypeptide as a substrate to another molecule. The present invention also features corresponding polynucleotide libraries comprising at least one polynucleotide sequence that encodes an antibody or antibody fragment of the invention. In specific embodiments, the library is provided on a nucleic acid array or in computer-readable format.

[0281] An antibody of the present invention may comprise a monoclonal antibody, polyclonal antibody, single chain antibody, intrabody, and active fragments of any of these. The active fragments include variable regions from either heavy chains or light chains. The antibody can comprise the backbone of a molecule with an immunoglobulin domain, e.g., a fibronectin backbone, a T-cell receptor backbone, or a CTLA4 backbone.

[0282] The present invention further features a targeting antibody, a neutralizing antibody, a stabilizing antibody, an enhancing antibody, an antibody agonist, an antibody antagonist, an antibody that promotes cellular endocytosis of a target antigen, a cytotoxic antibody, and an antibody that mediates antibody dependent cellular cytotoxicity (ADCC). The antibody that mediates ADCC can have a cytotoxic component, e.g., a radioisotope, a radioactive molecule, a microbial toxin, a plant toxin, a chemotherapeutic agent, or a chemical substance, such as doxorubicin or cisplatin. The invention also features an inhibitory antibody, functioning to specifically inhibit the binding of a cognate polypeptide to its ligand or its substrate, or to specifically inhibit the binding of a cognate peptide as the substrate of another molecule.

[0283] The antibodies of the present invention also encompass a human antibody, a non-human primate antibody, a monkey antibody, a non-primate animal antibody, e.g., a rodent antibody, rat antibody, a mouse antibody, a hamster antibody, a guinea pig antibody, a chicken antibody, a cattle antibody, a sheep antibody, a goat antibody, a horse antibody, porcine antibody, a cow antibody, a rabbit antibody, a cat

antibody, or a dog antibody. It also features a humanized antibody, a primatized antibody, and a chimeric antibody.

[0284] The antibodies of the invention can be produced *in vitro* or *in vivo*. For example, the present invention features an antibody produced in a cell-free expression system, a prokaryote expression system or a eukaryote expression system, as described herein.

[0285] The invention further provides a host cell that can produce an antibody of the invention or a fragment thereof. The antibody may also be secreted by the cell. The host cell can be a hybridoma, or a prokaryotic or eukaryotic cell. The invention also provides a bacteriophage or other virus particle comprising an antibody of the invention, or a fragment thereof. The bacteriophage or other virus particle may display the antibody or fragment thereof on its surface, and the bacteriophage itself may exist within a bacterial cell. The antibody may also comprise a fusion protein with a viral or bacteriophage protein.

[0286] The invention further provides transgenic multicellular organisms, e.g., plants or non-human animals, as well as tissues or organs, comprising a polynucleotide sequence encoding a subject antibody or fragment thereof. The organism, tissues, or organs will generally comprise cells producing an antibody of the invention, or a fragment thereof.

[0287] In another aspect, the present invention features a method of making an antibody by immunizing a host animal. In this method, a polypeptide or a fragment thereof, a polynucleotide encoding a polypeptide, or a polynucleotide encoding a fragment thereof, is introduced into an animal in a sufficient amount to elicit the generation of antibodies specific to the polypeptide or fragment thereof, and the resulting antibodies are recovered from the animal. The polypeptide can be encoded by a nucleic acid molecule comprising a nucleotide sequence chosen from at least one polynucleotide sequence according to SEQ ID NOS.: 1 - 104.

[0288] The invention thus also provides a non-human animal comprising an antibody of the invention. The animal can be a non-human primate, (e.g., a monkey) a rodent (e.g., a rat, a mouse, a hamster, a guinea pig), a chicken, cattle (e.g., a sheep, a goat, a horse, a pig, a cow), a rabbit, a cat, or a dog.

[0289] The present invention also features a method of making an antibody by isolating a spleen from an animal injected with a polypeptide or a fragment thereof, a polynucleotide encoding a polypeptide, or a polynucleotide encoding a

fragment thereof, and recovering antibodies from the spleen cells. Hybridomas can be made from the spleen cells, and hybridomas secreting specific antibodies can be selected.

[0290] The present invention further features a method of making a polynucleotide library from spleen cells, and selecting a cDNA clone that produces specific antibodies, or fragments thereof. The cDNA clone or a fragment thereof can be expressed in an expression system that allows production of the antibody or a fragment thereof, as provided herein.

[0291] The invention also provides a method for determining the presence or measuring the level of a polypeptide that specifically binds to an antibody of the invention. This method involves allowing the antibody to interact with a sample, and determining whether interaction between the antibody and any polypeptide in the sample has occurred. Antibodies that specifically bind to at least one subject polypeptide are useful in diagnostic assays, e.g., to detect the presence of a subject polypeptide. Similarly, the invention features a method of determining the presence of an antibody to a polypeptide of the invention, by providing the polypeptide, allowing the antibody and the polypeptide to interact, and determining whether interaction has occurred.

[0292] The present invention further features a method of identifying an agent that modulates the level of a subject polypeptide (or an mRNA encoding a subject polypeptide) in a cell. The method generally involves contacting a cell (e.g., a eukaryotic cell) that produces the subject polypeptide with a test agent; and determining the effect, if any, of the test agent on the level of the polypeptide in the cell.

[0293] The present invention further features a method of identifying an agent that modulates biological activity of a subject polypeptide. The methods generally involve contacting a subject polypeptide with a test agent; and determining the effect, if any, of the test agent on the activity of the polypeptide. In certain embodiments, the polypeptide is expressed on a cell surface. In certain embodiments, the agent or modulator is an antibody, for example, where an antibody binds to the polypeptide or affects its biological activity.

[0294] The present invention further features biologically active agents (or modulators) identified using a method of the invention.

[0295] The present invention also features a method of modulating biological activity using an agent selectable by the above methods. Briefly, the method of modulating biological activity comprises contacting the agent with a first human or a non-human host cell, thereby modulating the activity of the first host cell or a second host cell. In one example, contacting the agent with the first human or non-human host cell results in the recruitment of a second host cell. The agent may be an antibody or antibody fragment of the invention.

[0296] The modulation can comprise directly enhancing cell activity, indirectly enhancing cell activity, directly inhibiting cell activity, or indirectly inhibiting cell activity. The cell activity that is modulated can include transcription, translation, cell cycle control, signal transduction, intracellular trafficking, cell adhesion, cell mobility, proteolysis, ion transport, water transport, DNA repair, hydrolysis, lipase activity, polymerization using an RNA temple or a DNA template, and nuclease activity. The modulation can result in cell death or apoptosis, or inhibition of cell death or apoptosis, as well as cell growth, cell proliferation, or cell survival, or inhibition of cell growth, cell proliferation, or cell survival; as well as mucosal preservation, inhibition of eicosanoid synthesis, or resistance to infection by viruses.

[0297] Either the first or the second host cell can be a human or a non-human host cell. Either the first or the second host cell can be an immune cell, e.g., a T cell, B cell, NK cell, dendritic cell, macrophage, muscle cell, stem cell, skin cell, fat cell, blood cell, brain cell, bone marrow cell, endothelial cell, retinal cell, bone cell, kidney cell, pancreatic cell, liver cell, spleen cell, prostate cell, cervical cell, ovarian cell, breast cell, lung cell, liver cell, soft tissue cell, colorectal cell, other cell of the gastrointestinal tract, or a cancer cell.

[0298] The invention also provides a method of diagnosing cancer, proliferative, inflammatory, immune, viral, bacterial, or metabolic disorder in a patient, by allowing an antibody specific for a polypeptide of the invention to contact a patient sample, and detecting specific binding between the antibody and any antigen in the sample to determine whether the subject has cancer, proliferative, inflammatory, immune, viral, bacterial, or metabolic disorder.

[0299] The invention further provides a method of diagnosing cancer, proliferative, inflammatory, immune, viral, bacterial, or metabolic disorder in a patient, by allowing a polypeptide of the invention to contact a patient sample, and



detecting specific binding between the polypeptide and any interacting molecule in the sample to determine whether the subject has cancer, proliferative, inflammatory, immune, viral, bacterial, or metabolic disorder.

[0300] The invention also features a method of providing a polynucleotide, a polypeptide, or an agent of the invention, such as an antibody, to a subject by oral, buccal, nasal, rectal, intraperitoneal, intradermal, transdermal, intratracheal, intrathecal, or parenteral administration, or otherwise by implantation or inhalation. For example, the polynucleotide, polypeptide or agent can be administered intranasally, intravenously, intra-arterially, intracardiacally, subcutaneously, intraperitoneally, transdermally, intraventricularly, or intracranially. The invention also provides a method for formulating a polynucleotide, polypeptide, or modulator composition, such as an antibody composition, for delivery by any of the routes of administration provided above, for example, for treatment of disorders. For example, the parenteral delivery can be via inhalation or implantation. The parenteral delivery can also be oral, intranasal, intraventricular, or intracranial.

[0301] The present invention also features a pharmaceutical composition comprising a polynucleotide, polypeptide, or modulator of the invention and a carrier. The carrier can be a pharmaceutically acceptable carrier. The modulator can be obtainable by any methods of the invention, for example, the modulator can be an antibody or a fragment thereof. Further, oral formulations, preparations for injection, aerosol formulations, and suppositories can be prepared, each comprising the polynucleotide, polypeptide, or modulator composition. Further, nucleic acid compositions comprising polynucleotide sequences encoding the subject antibodies, or fragments thereof, can be prepared for administration to a subject.

[0302] The invention also features a non-human animal injected with the polynucleotide, polypeptide, or modulator composition, for example the antibody composition. Again, the animal can be a non-human primate, (e.g., a monkey) a rodent (e.g., a rat, a mouse, a hamster, a guinea pig), a chicken, cattle (e.g., a sheep, a goat, a horse, a pig, a cow), a rabbit, a cat, or a dog.

[0303] In another aspect, the invention provides a method of treating a disorder in a subject needing or desiring such treatment, comprising administering a polynucleotide, polypeptide, or modulator of the invention to the subject. The subject can be a human or a non-human animal. The disorder can be cancer, proliferative, inflammatory, immune, metabolic, ulcerative, bacterial, or viral disorders.

[0304] For example, the method of treatment may comprise administering an antibody composition with a first antibody that specifically binds to a first epitope of a first polypeptide or a fragment thereof, or that interferes with at least one activity of the first polypeptide or a fragment thereof, wherein the first polypeptide is encoded by a nucleic acid molecule comprising a nucleotide sequence chosen from SEQ ID NOS.: 1 - 104, or any nucleic acid of the present invention. In certain embodiments, this method further comprises using a second antibody that binds specifically to or interferes with the activity of a second epitope of the first polypeptide or to a first epitope of a second polypeptide. The second polypeptide can be encoded by a nucleic acid molecule comprising a nucleotide sequence chosen from SEQ ID NOS.: 1 - 104, or any nucleic acid of the present invention. In certain embodiments, the antibody binds, or interferes with the activity of, at least one polypeptide fragment, wherein the fragment is an extracellular fragment of the polypeptide, or an extracellular fragment of the polypeptide minus the signal peptide, for the treatment, for example, of proliferative disorders, such as cancer.

[0305] In other embodiments, the modulator may bind to a cell surface molecule that is over-expressed in the disorder. Further the modulator may be linked to an antibody of the invention. The antibody can be capable of initiating antibody dependent cell cytotoxicity, e.g., where the antibody is in turn coupled to cytotoxic agents. This method is applicable when the disorder is cancer, another proliferative disorder, inflammatory, immune, bacterial, viral, or metabolic disorder, and the cell surface molecule is over-expressed in a cancer cell, diseased cell or virus-infected cell. The cell surface molecule can be a single-transmembrane-related protein, a multiple-transmembrane-related protein, a kinase-related protein, a protein kinase-related protein, a ligase-related protein, a nuclear hormone receptor-related protein, a phosphatase-related protein, a protease-related protein, a phosphodiesterase-related protein, a kinesin-related protein, an immunoglobulin-related protein, a T-cell receptor-related protein, a glycosylphosphatidylinositol anchor-related protein, or other amino acid sequence, including, an activator-related protein, an adaptor-related protein, an adhesion molecule-related protein, an ATPase-related protein, an ATP-related protein, a breakpoint-related protein, a channel-related protein, a checkpoint-related protein, a complex-related protein, a dehydrogenase-related protein, a disintegrin-related protein, an endopeptidase-related protein, a germ-cell-related protein, a GTPase-related protein, a helicase-related protein, a hydrolase-related

protein, an integrase-related protein, an integrin-related protein, isomerase-related protein, a membrane-related protein, a mucin-related protein, an oxygenase-related protein, a peroxidase-related protein, a phospholipase-related protein, a prosaposin-related protein, a proteasome-related protein, a reductase-related protein, a reverse transcriptase-related protein, an RNase-related protein, an RNase H-related protein, an SH3-related protein, a synthetase-related protein, a TATA box-related protein, a Tat-related protein, a transferase-related protein, a transposase-related protein, a ubiquitin-related protein, or virus-related protein that is over-expressed in cancer, proliferative, inflammatory, immune, bacterial, viral, or metabolic disorder.

[0306] The invention also provides a method for prophylactic or therapeutic treatment of a subject needing or desiring such treatment by providing a vaccine, that can be administered to the subject. The vaccine may comprise one or more of a polynucleotide, polypeptide, or modulator of the invention, for example an antibody vaccine composition, a polypeptide vaccine composition, or a polynucleotide vaccine composition, useful for treating cancer, proliferative, inflammatory, immune, metabolic, bacterial, or viral disorders.

[0307] For example, the vaccine can be a cancer vaccine, and the polypeptide can concomitantly be a cancer antigen. The vaccine may be an anti-inflammatory vaccine, and the polypeptide can concomitantly be an inflammation-related antigen. The vaccine may be a viral vaccine, and the polypeptide can concomitantly be a viral antigen. In some embodiments, the vaccine comprises a polypeptide fragment, comprising at least one extracellular fragment of a polypeptide of the invention, and/or at least one extracellular fragment of a polypeptide of the invention minus the signal peptide, for the treatment, for example, of proliferative disorders, such as cancer. In certain embodiments, the vaccine comprises a polynucleotide encoding one or more such fragments, administered for the treatment, for example, of proliferative disorders, such as cancer. Further, the vaccine can be administered with or without an adjuvant.

[0308] In another aspect, the invention provides a method for gene therapy by providing a polynucleotide comprising a nucleic acid molecule encoding a polypeptide, such as an antibody of the invention, and administering the polynucleotide to a subject needing or desiring such treatment.

[0309] The invention further provides a kit comprising one or more of a polynucleotide, polypeptide, or modulator composition, such as an antibody

composition, which may include instructions for its use. Such kits are useful in diagnostic applications, for example, to detect the presence and/or level of a polypeptide in a biological sample by specific antibody interaction.

## MODES FOR CARRYING OUT THE INVENTION

### Brief Description of the Table

[0310] Each sequence shown in Table 1 is identified by a Five Prime Therapeutics, Inc. (FP) identification number (FP ID). Each protein in Table 1 is also described by an annotation of the Fantom mouse protein with the greatest degree of similarity to the claimed sequences. The Fantom database was compiled by the Fantom Consortium and is accessible, for example, at <http://fantom.gsc.riken.go.jp/db/> (Bono et al., 2002). It provides curated functional annotation to full-length mouse sequences (Okzaki et al., 2002). The similarities of the claimed sequences of the invention with the annotated sequences in Table 1 suggest that they may share structural and functional properties, and exhibit similar expression profiles and localizations.

### Definitions

[0311] "Related sequences" include nucleotide and amino acid sequences that are involved in the function of their referent. For example, "receptor-related sequences" include all sequences that are involved in receptor function. This includes, but is not limited to, sequences that are involved in receptor synthesis, receptor regulation, receptor effector function, and receptor degradation. "Related sequences" also encompass complementary nucleic acid sequences, and biologically active fragments of nucleic acid and amino acid sequences.

[0312] The terms "polynucleotide," "nucleotide," "nucleic acid," "polynucleic molecule," "nucleotide molecule," "nucleic acid molecule," "nucleic acid sequence," "polynucleotide sequence," and "nucleotide sequence" are used interchangeably herein to refer to polymeric forms of nucleotides of any length. The polynucleotides can contain deoxyribonucleotides, ribonucleotides, and/or their analogs or derivatives. For example, nucleic acids can be naturally occurring DNA or RNA, or can be synthetic analogs, as known in the art. The terms also encompass genomic DNA, genes, gene fragments, exons, introns, regulatory sequences or regulatory elements (such as promoters, enhancers, initiation and termination regions, other control regions, expression regulatory factors, and expression controls), DNA

comprising one or more single-nucleotide polymorphisms (SNPs), allelic variants, isolated DNA of any sequence, and cDNA. The terms also encompass mRNA, tRNA, rRNA, ribozymes, splice variants, antisense RNA, antisense conjugates, RNAi, and isolated RNA of any sequence. The terms also encompass recombinant polynucleotides, heterologous polynucleotides, branched polynucleotides, labeled polynucleotides, hybrid DNA/RNA, polynucleotide constructs, vectors comprising the subject nucleic acids, nucleic acid probes, primers, and primer pairs. The polynucleotides can comprise modified nucleic acid molecules, with alterations in the backbone, sugars, or heterocyclic bases, such as methylated nucleic acid molecules, peptide nucleic acids, and nucleic acid molecule analogs, which may be suitable as, for example, probes if they demonstrate superior stability and/or binding affinity under assay conditions. Analogs of purines and pyrimidines, including radiolabeled and fluorescent analogs, are known in the art. The polynucleotides can have any three-dimensional structure, and can perform any function, known or as yet unknown. The terms also encompass single-stranded, double-stranded and triple helical molecules that are either DNA, RNA, or hybrid DNA/RNA and that may encode a full-length gene or a biologically active fragment thereof. Biologically active fragments of polynucleotides can encode the polypeptides herein, as well as anti-sense and RNAi molecules. Thus, the full length polynucleotides herein may be treated with enzymes, such as Dicer, to generate a library of short RNAi fragments which are within the scope of the present invention.

[0313] The novel polynucleotides herein include those shown in the Table, SEQ ID NOS.: 1-104, and biologically active fragments thereof. The polynucleotides also include modified, labeled, and degenerate variants of the nucleic acid sequences, as well as nucleic acid sequences that are substantially similar or homologous to nucleic acids encoding the subject proteins.

[0314] A "biologically active" entity, or an entity having "biological activity," is one having structural, regulatory, or biochemical functions of a naturally occurring molecule or any function related to or associated with a metabolic or physiological process. Biologically active polynucleotide fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a polynucleotide of the present invention. The biological activity can include an improved desired activity, or a decreased undesirable activity. For example, an entity demonstrates biological activity when it participates in a molecular interaction with

another molecule, or when it has therapeutic value in alleviating a disease condition, or when it has prophylactic value in inducing an immune response to the molecule, or when it has diagnostic value in determining the presence of the molecule, such as a biologically active fragment of a polynucleotide that can be detected as unique for the polynucleotide molecule, or that can be used as a primer in PCR.

[0315] The term "degenerate variant" of a nucleic acid sequence refers to all nucleic acid sequences that can be directly translated, according to the standard genetic code, to provide an amino acid sequence identical to that translated from a reference nucleic acid sequence.

[0316] The term "gene" or "genomic sequence" as used herein is an open reading frame encoding specific proteins and polypeptides, for example, an mRNA, cDNA, or genomic DNA, and also may or may not include intervening introns, or adjacent 5' and 3' non-coding nucleotide sequences involved in the regulation of expression up to about 20 kb beyond the coding region, and possibly further in either direction. A gene can be introduced into an appropriate vector for extrachromosomal maintenance or for integration into a host genome.

[0317] The term "transgene" as used herein is a nucleic acid sequence that is incorporated into a transgenic organism. A "transgene" can contain one or more transcriptional regulatory sequences, and other sequences, such as introns, that may be useful for expressing or secreting the nucleic acid or fusion protein it encodes.

[0318] The term "cDNA" as used herein is intended to include all nucleic acids that share the sequence elements of mature mRNA species, where sequence elements are exons and 3' and 5' non-coding regions. Generally, mRNA species have contiguous exons, the intervening introns having been removed by nuclear RNA splicing to create a continuous open reading frame encoding a protein.

[0319] The term "splice variant" refers to all types of RNAs transcribed from a given gene that when processed collectively encode plural protein isoforms. The term "alternative splicing" and related terms refer to all types of RNA processing that lead to expression of plural protein isoforms from a single gene. Some genes are first transcribed as long mRNA precursors that are then shortened by a series of processing steps to produce the mature mRNA molecule. One of these steps is RNA splicing, in which the intron sequences are removed from the mRNA precursor. A cell can splice the primary transcript in different ways, making different "splice variants," and thereby making different polypeptide chains from the same gene, or from the same

mRNA molecule. Splice variants can include, for example, exon insertions, exon extensions, exon truncations, exon deletions, alternatives in the 5' untranslated region and alternatives in the 3' untranslated region.

[0320] "Oligonucleotide" may generally refer to polynucleotides of between about 5 and about 100 nucleotides of single- or double-stranded nucleic acids. For the purposes of this disclosure, there is no upper limit to the length of an oligonucleotide. Oligonucleotides are also known as oligomers or oligos and can be isolated from genes, or chemically synthesized by methods known in the art.

[0321] "Nucleic acid composition" as used herein is a composition comprising a nucleic acid sequence, including one having an open reading frame that encodes a polypeptide and is capable, under appropriate conditions, of being expressed as a polypeptide. The term includes, for example, vectors, including plasmids, cosmids, viral vectors (e.g., retrovirus vectors such as lentivirus, adenovirus, and the like), human, yeast, bacterial, P1-derived artificial chromosomes (HAC's, YAC's, BAC's, PAC's, etc), and mini-chromosomes, *in vitro* host cells, *in vivo* host cells, tissues, organs, allogenic or congenic grafts or transplants, multicellular organisms, and chimeric, genetically modified, or transgenic animals comprising a subject nucleic acid sequence.

[0322] An "isolated," "purified," or "substantially isolated" polynucleotide, or a polynucleotide in "substantially pure form," in "substantially purified form," in "substantial purity," or as an "isolate," is one that is substantially free of the sequences with which it is associated in nature, or other nucleic acid sequences that do not include a sequence or fragment of the subject polynucleotides. By substantially free is meant that less than about 90%, less than about 80%, less than about 70%, less than about 60%, or less than about 50% of the composition is made up of materials other than the isolated polynucleotide. For example, the isolated polynucleotide is at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% free of the materials with which it is associated in nature. For example, an isolated polynucleotide may be present in a composition wherein at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, at least about 99% of the total macromolecules (for example, polypeptides, fragments thereof, polynucleotides, fragments thereof, lipids, polysaccharides, and oligosaccharides) in the composition is the isolated

polynucleotide. Where at least about 99% of the total macromolecules is the isolated polynucleotide, the polynucleotide is at least about 99% pure, and the composition comprises less than about 1% contaminant. As used herein, an "isolated," "purified" or "substantially isolated" polynucleotide, or a polynucleotide in "substantially pure form," in "substantially purified form," in "substantial purity," or as an "isolate," also refers to recombinant polynucleotides, modified, degenerate and homologous polynucleotides, and chemically synthesized polynucleotides, which, by virtue of origin or manipulation, are not associated with all or a portion of a polynucleotide with which it is associated in nature, are linked to a polynucleotide other than that to which it is linked in nature, or do not occur in nature. For example, the subject polynucleotides are generally provided as other than on an intact chromosome, and recombinant embodiments are typically flanked by one or more nucleotides not normally associated with the subject polynucleotide on a naturally-occurring chromosome.

[0323] The terms "polypeptide," "peptide," and "protein," used interchangeably herein, refer to a polymeric form of amino acids of any length, which can include naturally-occurring amino acids, coded and non-coded amino acids, chemically or biochemically modified, derivatized, or designer amino acids, amino acid analogs, peptidomimetics, and depsi-peptides, and polypeptides having modified, cyclic, bicyclic, depsi-cyclic, or depsi-bicyclic peptide backbones. The term includes single chain protein as well as multimers. The term also includes conjugated proteins, fusion proteins, including, but not limited to, GST fusion proteins, fusion proteins with a heterologous amino acid sequence, fusion proteins with heterologous and homologous leader sequences, fusion proteins with or without N-terminal methionine residues, pegylated proteins, and immunologically tagged proteins. Also included in this term are variations of naturally occurring proteins, where such variations are homologous or substantially similar to the naturally occurring protein, as well as corresponding homologs from different species. Variants of polypeptide sequences include insertions, additions, deletions, or substitutions compared with the subject polypeptides. The term also includes peptide aptamers.

[0324] The novel polypeptides herein include amino acid sequences encoded by an open reading frame (ORF), described in greater detail below, including the full length protein and fragments thereof, particularly biologically active fragments and/or fragments corresponding to functional domains, e.g., a signal peptide or leader



sequence, an enzyme active site, including a cleavage site and an enzyme catalytic site, a domain for interaction with other protein(s), a domain for binding DNA, a regulatory domain, a consensus domain that is shared with other members of the same protein family, such as a kinase family or an immunoglobulin family; an extracellular domain that may act as a target for antibody production or that may be cleaved to become a soluble receptor or a ligand for a receptor; an intracellular fragment of a transmembrane protein that participates in signal transduction; a transmembrane domain of a transmembrane protein that may facilitate water or ion transport; a sequence associated with cell survival and/or cell proliferation; a sequence associated with cell cycle arrest, DNA repair and/or apoptosis; a sequence associated with a disease or disease prognosis, including types of cancer, degenerative disease, inflammatory disease, immunological disease, genetic disease, metabolic disease, and/or viral infection; and including fusions of the subject polypeptides to other proteins or parts thereof; modifications of the subject polypeptide, e.g., comprising modified, derivatized, or designer amino acids, modified peptide backbones, and/or immunological tags; as well as intra- and inter-species homologs of the subject polypeptides.

[0325] As noted above, a "biologically active" entity, or an entity having "biological activity," is one having structural, regulatory, or biochemical functions of a naturally occurring molecule or any function related to or associated with a metabolic or physiological process. Biologically active polypeptide fragments are those exhibiting activity similar, but not necessarily identical, to an activity of a polypeptide of the present invention. The biological activity can include an improved desired activity, or a decreased undesirable activity. For example, an entity demonstrates biological activity when it participates in a molecular interaction with another molecule, or when it has therapeutic value in alleviating a disease condition, or when it has prophylactic value in inducing an immune response to the molecule, or when it has diagnostic value in determining the presence of the molecule. A biologically active polypeptide or fragment thereof includes one that can participate in a biological reaction, for example, as a transcription factor that combines with other transcription factors for initiation of transcription, or that can serve as an epitope or immunogen to stimulate an immune response, such as production of antibodies, or that can transport molecules into or out of cells, or that can perform a catalytic activity, for example polymerization or nuclease activity, or that can participate in

signal transduction by binding to receptors, proteins, or nucleic acids, activating enzymes or substrates.

[0326] A "signal peptide," or a "leader sequence," comprises a sequence of amino acid residues, typically, at the N terminus of a polypeptide, which directs the intracellular trafficking of the polypeptide. Polypeptides that contain a signal peptide or leader sequence typically also contain a signal peptide or leader sequence cleavage site. Such polypeptides, after cleavage at the cleavage sites, generate mature polypeptides, for example, after extracellular secretion or after being directed to the appropriate intracellular compartment.

[0327] "Depsipeptides" are compounds containing a sequence of at least two alpha-amino acids and at least one alpha-hydroxy carboxylic acid, which are bound through at least one normal peptide link and ester links, derived from the hydroxy carboxylic acids. "Linear depsipeptides" can comprise rings formed through S-S bridges, or through an hydroxy or a mercapto group of an hydroxy-, or mercapto-amino acid and the carboxyl group of another amino- or hydroxy-acid but do not comprise rings formed only through peptide or ester links derived from hydroxy carboxylic acids. "Cyclic depsipeptides" are peptides containing at least one ring formed only through peptide or ester links, derived from hydroxy carboxylic acids.

[0328] An "isolated," "purified," or "substantially isolated" polypeptide, or a polypeptide in "substantially pure form," in "substantially purified form," in "substantial purity," or as an "isolate," is one that is substantially free of the materials with which it is associated in nature or other polypeptide sequences that do not include a sequence or fragment of the subject polypeptides. By substantially free is meant that less than about 90%, less than about 80%, less than about 70%, less than about 60%, or less than about 50% of the composition is made up of materials other than the isolated polypeptide. For example, the isolated polypeptide is at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% free of the materials with which it is associated in nature. For example, an isolated polypeptide may be present in a composition wherein at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 90%, at least about 95%, at least about 97%, or at least about 99% of the total macromolecules (for example, polypeptides, fragments thereof, polynucleotides, fragments thereof, lipids, polysaccharides, and oligosaccharides) in the composition is the isolated polypeptide. Where at least about

99% of the total macromolecules is the isolated polypeptide, the polypeptide is at least about 99% pure, and the composition comprises less than about 1% contaminant. As used herein, an "isolated," "purified," or "substantially isolated" polypeptide, or a polypeptide in "substantially pure form," in "substantially purified form," in "substantial purity," or as an "isolate," also refers to recombinant polypeptides, modified, tagged and fusion polypeptides, and chemically synthesized polypeptides, which by virtue of origin or manipulation, are not associated with all or a portion of the materials with which they are associated in nature, are linked to molecules other than that to which they are linked in nature, or do not occur in nature.

[0329] Detection methods of the invention can be qualitative or quantitative. Thus, as used herein, the terms "detection," "identification," "determination," and the like, refer to both qualitative and quantitative determinations, and include "measuring." For example, detection methods include methods for detecting the presence and/or level of polynucleotide or polypeptide in a biological sample, and methods for detecting the presence and/or level of biological activity of polynucleotide or polypeptide in a sample.

[0330] As used herein, the term "array" or "microarray" may be used interchangeably and refers to a collection of plural biological molecules such as nucleic acids, polypeptides, or antibodies, having locatable addresses that may be separately detectable. Generally, "microarray" encompasses use of sub microgram quantities of biological molecules. The biological molecules may be affixed to a substrate or may be in solution or suspension. The substrate can be porous or solid, planar or non-planar, unitary or distributed, such as a glass slide, a 96 well plate, with or without the use of microbeads or nanobeads. As such, the term "microarray" includes all of the devices referred to as microarrays in Schena, 1999; Bassett et al., 1999; Bowtell, 1999; Brown and Botstein, 1999; Chakravarti, 1999; Cheung et al., 1999; Cole et al., 1999; Collins, 1999; Debouck and Goodfellow, 1999; Duggan et al., 1999; Hacia, 1999; Lander, 1999; Lipshutz et al., 1999; Southern, et al., 1999; Schena, 2000; Brenner et al, 2000; Lander, 2001; Steinhaur et al., 2002; and Espejo et al, 2002. Nucleic acid microarrays include both oligonucleotide arrays (DNA chips) containing expressed sequence tags ("ESTs") and arrays of larger DNA sequences representing a plurality of genes bound to the substrate, either one of which can be used for hybridization studies. Protein and antibody microarrays include arrays of polypeptides or proteins, including but not limited to, polypeptides or proteins

obtained by purification, fusion proteins, and antibodies, and can be used for specific binding studies (Zhu and Snyder, 2003; Houseman et al., 2002; Schaeferling et al., 2002; Weng et al., 2002; Winssinger et al., 2002; Zhu et al., 2001; Zhu et al. 2001; and MacBeath and Schreiber, 2000).

[0331] A "nucleic acid hybridization reaction" is one in which single strands of DNA or RNA randomly collide with one another, and bind to each other only when their nucleotide sequences have some degree of complementarity. The solvent and temperature conditions can be varied in the reactions to modulate the extent to which the molecules can bind to one another. Hybridization reactions can be performed under different conditions of "stringency." The "stringency" of a hybridization reaction as used herein refers to the conditions (e.g., solvent and temperature conditions) under which two nucleic acid strands will either pair or fail to pair to form a "hybrid" helix.

[0332] " $T_m$ " is the temperature in degrees Celsius at which 50% of a polynucleotide duplex made of complementary strands of nucleic acids that are hydrogen bonded in an anti-parallel direction by Watson-Crick base pairing dissociate into single strands under conditions of the hybridization reaction.  $T_m$  can be predicted according to a standard formula, such as:  $T_m = 81.5 + 16.6 \log[X^+] + 0.41 (\%G/C) - 0.61 (\%F) - 600/L$ , where  $[X^+]$  is the cation concentration (usually sodium ion,  $Na^+$ ) in mol/L; (%G/C) is the number of G and C residues as a percentage of total residues in the duplex; (%F) is the percent formamide in solution (wt/vol); and L is the number of nucleotides in each strand of the paired nucleic acids.

[0333] A "buffer" is a system that tends to resist change in pH when a given increment of hydrogen ion or hydroxide ion is added. Buffered solutions contain conjugate acid-base pairs. Any conventional buffer can be used with the inventions herein including but not limited to, for example, Tris, phosphate, imidazole, and bicarbonate.

[0334] A "library" of polynucleotides comprises a collection of sequence information of a plurality of polynucleotide sequences, which information is provided in either biochemical form (e.g., as a collection of polynucleotide molecules), or in electronic form (e.g., as a collection of polynucleotide sequences stored in a computer-readable form, as in a computer-based system, a computer data file, and/or as part of a computer program).

[0335] A "library" of polypeptides comprises a collection of sequence information of a plurality of polypeptide sequences, which information is provided in, e.g., a collection of polypeptide sequences stored in a computer-readable form, as in a computer-based system, a computer data file, and/or as part of a computer program.

[0336] "Media" refers to a manufacture, other than an isolated nucleic acid molecule, that contains the sequence information of the present invention. Such a manufacture provides the genome sequence or a subset thereof in a form that can be examined by means not directly applicable to the sequence as it exists in a nucleic acid, e.g., with computer-readable media comprising data storage structures. Such media include, but are not limited to: magnetic storage media, such as a floppy disc, a hard disc storage medium, and a magnetic tape; optical storage media such as CD-ROM; electrical storage media such as RAM and ROM; and hybrids of these categories such as magnetic/optical storage media.

[0337] "Recorded" refers to a process for storing information on computer readable media, using any such methods as known in the art.

[0338] As used herein, "a computer-based system" refers to the hardware means, software means, and data storage means used to analyze the nucleotide sequence information of the present invention. The minimum hardware of the computer-based systems of the present invention comprises a central processing unit (CPU), input means, output means, and data storage means. A skilled artisan can readily appreciate that any one of the currently available computer-based systems are suitable for use in the present invention. The data storage means can comprise any manufacture comprising a recording of the present sequence information as described above, or a memory access means that can access such a manufacture.

[0339] "Search means" refers to one or more programs implemented on the computer-based system, to compare a target sequence or target structural motif, or expression levels of a polynucleotide in a sample, with the stored sequence information. A variety of known algorithms are publicly known and commercially available, e.g., MacPattern (EMBL), BLAST, BLASTN and BLASTX (NCBI), gapped BLAST, BLAZE, the Wise package, FASTX, Clustalw, FASTA, FASTA3, Align0, Toffee, BestFit, FastDB, and TeraBLAST (TimeLogic, Crystal Bay, Nevada). Search means can be used to identify fragments or regions of the genome that match a particular target sequence or target motif, for example, based on

sequence similarity, for example, to identify open reading frames (ORFs) within the genome that contain homology to ORFs from other organisms.

[0340] "Sequence similarity," "sequence homology," "homology," "sequence identity," and "percent sequence identity," used interchangeably herein, describe the degree of relatedness between two polynucleotide or polypeptide sequences. In general, "identity" means the exact match-up of two or more nucleotide sequences or two or more amino acid sequences, where the nucleotide or amino acids being compared are the same. Also, in general, "similarity" or "homology" means the exact match-up of two or more nucleotide sequences or two or more amino acid sequences, where the nucleotide or amino acids being compared are either the same or possess similar chemical and/or physical properties. The terms also refer to the percentage of the "aligned" bases (for the polynucleotides) or amino acid residues (for the polypeptides) that are identical when the sequences are aligned. Sequences can be aligned in a number of different ways and sequence similarity can be determined in a number of different ways. For example, the bases or amino acid residues of one sequence can be aligned to a gap in the other sequence, or they can be aligned only to another base or amino acid residue in the other sequence. A gap can range anywhere from one nucleotide, base, or amino acid residue to multiple exons in length, up to any number of nucleotides or amino acid residues. Further, sequences can be aligned such that nucleotides (or bases) align with nucleotides, nucleotides align with amino acid residues, or amino acid residues align with amino acid residues.

[0341] A "target sequence" can be any polynucleotide or amino acid sequence of six or more contiguous nucleotides or two or more amino acids, for example, from about 5 or from about 10 to about 100 amino acids, or from about 15 or from about 30 to about 300 nucleotides. A variety of comparing means can be used to accomplish comparison of sequence information from a sample (e.g., to analyze target sequences, target motifs, or relative expression levels) with the data storage means. A skilled artisan can readily recognize that any one of the publicly available homology search programs can be used as the search means for the computer based systems of the present invention to accomplish comparison of target sequences and motifs. Computer programs to analyze expression levels in a sample and in controls are also known in the art. A "target sequence" includes an "antibody target sequence," which refers to an amino acid sequence that can be used as an

immunogen for injection into animals for production of antibodies or for screening against a phage display or antibody library for identification of binding partners.

[0342] A "target structural motif," or "target motif," refers to any rationally selected sequence or combination of sequences in which the sequence(s) are chosen based on a three-dimensional configuration that is formed upon the folding of the target motif, or on consensus sequences of regulatory or active sites. There are a variety of target motifs known in the art. Protein target motifs include, but are not limited to, enzyme active sites and signal sequences. Nucleic acid target motifs include, but are not limited to, hairpin structures, promoter sequences, and other expression elements such as binding sites for transcription factors.

[0343] A "matrix" is a geometric network of antibody molecules and their antigens, as found in immunoprecipitation and flocculation reactions. An antibody matrix can exist in solution or on a solid phase support.

[0344] The term "binds specifically," in the context of antibody binding, refers to high avidity and/or high affinity binding of an antibody to a specific polypeptide, or more accurately, to an epitope of a specific polypeptide. Antibody binding to such epitope on a polypeptide can be stronger than binding of the same antibody to any other epitopes, particularly other epitopes that can be present in molecules in association with, or in the same sample as the polypeptide of interest. For example, when an antibody binds more strongly to one epitope than to another, adjusting the binding conditions can result in antibody binding almost exclusively to the specific epitope and not to any other epitopes on the same polypeptide, and not to any other polypeptide, which does not comprise the epitope. Antibodies that bind specifically to a subject polypeptide may be capable of binding other polypeptides at a weak, yet detectable, level (e.g., 10% or less of the binding shown to the polypeptide of interest). Such weak binding, or background binding, is readily discernible from the specific antibody binding to a subject polypeptide, e.g., by use of appropriate controls. In general, antibodies of the invention bind to a specific polypeptide with a binding affinity of  $10^{-7}$  M or greater (e.g.,  $10^{-8}$  M,  $10^{-9}$  M,  $10^{-10}$ ,  $10^{-11}$ , etc.).

[0345] The term "host cell" includes an individual cell, cell line, cell culture, or *in vivo* cell, which can be or has been a recipient of any polynucleotides or polypeptides of the invention, for example, a recombinant vector, an isolated polynucleotide, antibody or fusion protein. Host cells include progeny of a single host cell, and the progeny may not necessarily be completely identical (in

morphology, physiology, or in total DNA, RNA, or polypeptide complement) to the original parent cell due to natural, accidental, or deliberate mutation and/or change. Host cells can be prokaryotic or eukaryotic, including mammalian, insect, amphibian, reptile, crustacean, avian, fish, plant and fungal cells. A host cell includes cells transformed, transfected, transduced, or infected *in vivo* or *in vitro* with a polynucleotide of the invention, for example, a recombinant vector. A host cell which comprises a recombinant vector of the invention may be called a "recombinant host cell."

[0346] "Biological sample," "patient sample," "clinical sample" "sample," or "biological specimen," used interchangeably herein, encompasses a variety of sample types obtained from an individual, including biological fluids such as blood, serum, plasma, urine, cerebrospinal fluid, tears, saliva, lymph, dialysis fluid, lavage fluid, semen, and other liquid samples or tissues of biological origin. It includes tissue samples and tissue cultures or cells derived therefrom and the progeny thereof, including cells in culture, cell supernatants, and cell lysates. It includes organ or tissue culture derived fluids, tissue biopsy samples, tumor biopsy samples, stool samples, and fluids extracted from physiological tissues. Cells dissociated from solid tissues, tissue sections, and cell lysates are included. The definition also includes samples that have been manipulated in any way after their procurement, such as by treatment with reagents, solubilization, or enrichment for certain components, such as polynucleotides or polypeptides. Also included in the term are derivatives and fractions of biological samples. A biological sample can be used in a diagnostic, monitoring, or screening assay.

[0347] The terms "individual," "host," "patient," and "subject," used interchangeably herein, refer to a mammal, including, but not limited to, murines, simians, humans, felines, canines, equines, bovines, porcines, ovines, caprines, mammalian farm animals, mammalian sport animals, and mammalian pets. "Mammals" or "mammalian," are used broadly to describe organisms which are within the class mammalia, including the orders carnivore (*e.g.*, dogs and cats), rodentia (*e.g.*, mice, guinea pigs, and rats), and other mammals, including cattle, goats, sheep, cows, horses, rabbits, and pigs, and primates (*e.g.*, humans, chimpanzees, and monkeys).

[0348] The terms "agent," "substance," "modulator," and "compound" are used interchangeably herein. These terms refer to a substance that binds to or



modulates a level or activity of a subject polypeptide or a level of mRNA encoding a subject protein or nucleic acid, or that modulates the activity of a cell containing the subject protein or nucleic acid. Where the agent modulates a level of mRNA encoding a subject protein, agents include ribozymes, antisense, and RNAi molecules. Where the agent is a substance that modulates a level of activity of a subject polypeptide, agents include antibodies specific for the subject polypeptide, peptide aptamers, small molecules, agents that bind a ligand-binding site in a subject polypeptide, and the like. Antibody agents include antibodies that specifically bind a subject polypeptide and activate the polypeptide, such as receptor-ligand binding that initiates signal transduction; antibodies that specifically bind a subject polypeptide and inhibit binding of another molecule to the polypeptide, thus preventing activation of a signal transduction pathway; antibodies that bind a subject polypeptide to modulate transcription; antibodies that bind a subject polypeptide to modulate translation; as well as antibodies that bind a subject polypeptide on the surface of a cell to initiate antibody-dependent cytotoxicity ("ADCC") or to initiate cell killing or cell growth. Small molecule agents include those that bind the polypeptide to modulate activity of the polypeptide or cell containing the polypeptide in a similar fashion. The term "agent" also refers to substances that modulate a condition or disorder associated with a subject polynucleotide or polypeptide. Such agents include subject polynucleotides themselves, subject polypeptides themselves, and the like. Agents may be chosen from amongst candidate agents, as defined below.

[0349] The terms "candidate agent," "subject agent," or "test agent," used interchangeably herein, encompass numerous chemical classes, typically synthetic, semi-synthetic, or naturally occurring inorganic or organic molecules, small molecules, or macromolecular complexes. Candidate agents can be small organic compounds having a molecular weight of more than about 50 and less than about 2,500 daltons. Candidate agents can comprise functional groups necessary for structural interaction with proteins, particularly hydrogen bonding, and can include at least an amine, carbonyl, hydroxyl or carboxyl group, and can contain at least two of the functional chemical groups. The candidate agents can comprise cyclical carbon or heterocyclic structures and/or aromatic or polyaromatic structures substituted with one or more of the above functional groups. Candidate agents are also found among biomolecules, including oligonucleotides, polynucleotides, and fragments thereof, depsipeptides, polypeptides and fragments thereof, oligosaccharides, polysaccharides

and fragments thereof, lipids, fatty acids, steroids, purines, pyrimidines, derivatives thereof, structural analogs, modified nucleic acids, modified, derivatized or designer amino acids, or combinations thereof.

[0350] An "agent which modulates a biological activity of a subject polypeptide," as used herein, describes any substance, synthetic, semi-synthetic, or natural, organic or inorganic, small molecule or macromolecular, pharmaceutical or protein, with the capability of altering a biological activity of a subject polypeptide or of a fragment thereof, as described herein. Generally, a plurality of assay mixtures is run in parallel with different agent concentrations to obtain a differential response to the various concentrations. Typically, one of these concentrations serves as a negative control, i.e., at zero concentration or below the level of detection. The biological activity can be measured using any assay known in the art.

[0351] An agent which modulates a biological activity of a subject polypeptide increases or decreases the activity at least about 10%, at least about 15%, at least about 20%, at least about 25%, at least about 50%, at least about 100%, or at least about 2-fold, at least about 5-fold, or at least about 10-fold or more when compared to a suitable control.

[0352] The term "agonist" refers to a substance that mimics the function of an active molecule. Agonists include, but are not limited to, drugs, hormones, antibodies, and neurotransmitters, as well as analogues and fragments thereof.

[0353] The term "antagonist" refers to a molecule that competes for the binding sites of an agonist, but does not induce an active response. Antagonists include, but are not limited to, drugs, hormones, antibodies, and neurotransmitters, as well as analogues and fragments thereof.

[0354] The term "receptor" refers to a polypeptide that binds to a specific extracellular molecule and may initiate a cellular response.

[0355] The term "ligand" refers to any molecule that binds to a specific site on another molecule.

[0356] The term "modulate" encompasses an increase or a decrease, a stimulation, inhibition, or blockage in the measured activity when compared to a suitable control. "Modulation" of expression levels includes increasing the level and decreasing the level of an mRNA or polypeptide encoded by a polynucleotide of the invention when compared to a control lacking the agent being tested. In some embodiments, agents of particular interest are those which inhibit a biological activity

of a subject polypeptide, and/or which reduce a level of a subject polypeptide in a cell, and/or which reduce a level of a subject mRNA in a cell and/or which reduce the release of a subject polypeptide from a eukaryotic cell. In other embodiments, agents of interest are those that increase a biological activity of a subject polypeptide, and/or which increase a level of a subject polypeptide in a cell, and/or which increase a level of a subject mRNA in a cell and/or which increase the release of a subject polypeptide from a eukaryotic cell.

[0357] An agent that "modulates the level of expression of a nucleic acid" in a cell is one that brings about an increase or decrease of at least about 1.25-fold, at least about 1.5-fold, at least about 2-fold, at least about 5-fold, at least about 10-fold, or more in the level (i.e., an amount) of mRNA and/or polypeptide following cell contact with a candidate agent compared to a control lacking the agent.

[0358] "Modulating a level of active subject polypeptide" includes increasing or decreasing activity of a subject polypeptide; increasing or decreasing a level of active polypeptide protein; increasing or decreasing a level of mRNA encoding active subject polypeptide, and increasing or decreasing the release of subject polypeptide for a eukaryotic cell. In some embodiments, an agent is a subject polypeptide, where the subject polypeptide itself is administered to an individual. In some embodiments, an agent is an antibody specific for a subject polypeptide. In some embodiments, an agent is a chemical compound such as a small molecule that may be useful as an orally available drug. Such modulation includes the recruitment of other molecules that directly effect the modulation. For example, an antibody that modulates the activity of a subject polypeptide that is a receptor on a cell surface may bind to the receptor and fix complement, activating the complement cascade and resulting in lysis of the cell.

[0359] The term "over-expressed" refers to a state wherein there exists any measurable increase over normal or baseline levels. For example, a molecule that is over-expressed in a disorder is one that is manifest in a measurably higher level compared to levels in the absence of the disorder.

[0360] "Treatment," "treating," and the like, as used herein, refer to obtaining a desired pharmacologic and/or physiologic effect, covering any treatment of a pathological condition or disorder in a mammal, including a human. The effect may be prophylactic in terms of completely or partially preventing a disorder or symptom thereof and/or may be therapeutic in terms of a partial or complete cure for

a disorder and/or adverse affect attributable to the disorder. That is, "treatment" includes (1) preventing the disorder from occurring or recurring in a subject who may be predisposed to the disorder but has not yet been diagnosed as having it, (2) inhibiting the disorder, such as arresting its development, (3) stopping or terminating the disorder or at least symptoms associated therewith, so that the host no longer suffers from the disorder or its symptoms, such as causing regression of the disorder or its symptoms, for example, by restoring or repairing a lost, missing or defective function, or stimulating an inefficient process, or (4) relieving, alleviating, or ameliorating the disorder, or symptoms associated therewith, where ameliorating is used in a broad sense to refer to at least a reduction in the magnitude of a parameter, such as inflammation, pain, and/or tumor size.

- [0361] A "pharmaceutically acceptable carrier," "pharmaceutically acceptable diluent," or "pharmaceutically acceptable excipient," or "pharmaceutically acceptable vehicle," used interchangeably herein, refer to a non-toxic solid, semisolid or liquid filler, diluent, encapsulating material or formulation auxiliary of any conventional type. A pharmaceutically acceptable carrier is non-toxic to recipients at the dosages and concentrations employed and is compatible with other ingredients of the formulation. For example, the carrier for a formulation containing polypeptides would not normally include oxidizing agents and other compounds that are known to be deleterious to polypeptides. Suitable carriers include, but are not limited to, water, dextrose, glycerol, saline, ethanol, and combinations thereof. The carrier can contain additional agents such as wetting or emulsifying agents, pH buffering agents, or adjuvants which enhance the effectiveness of the formulation. Adjuvants of the invention include, but are not limited to Freund's, Montanide ISA Adjuvants [Seppic, Paris, France], Ribi's Adjuvants (Ribi ImmunoChem Research, Inc., Hamilton, MT), Hunter's TiterMax (CytRx Corp., Norcross, GA), Aluminum Salt Adjuvants (Alhydrogel - Superfos of Denmark/Accurate Chemical and Scientific Co., Westbury, NY), Nitrocellulose-Adsorbed Protein, Encapsulated Antigens, and Gerbu Adjuvant (Gerbu Biotechnik GmbH, Gaiberg, Germany/C-C Biotech, Poway, CA). Topical carriers include liquid petroleum, isopropyl palmitate, polyethylene glycol, ethanol (95%), polyoxyethylene monolaurate (5%) in water, or sodium lauryl sulfate (5%) in water. Other materials such as anti-oxidants, humectants, viscosity stabilizers, and similar agents can be added as necessary. Percutaneous penetration enhancers such as Azone can also be included.

[0362] "Pharmaceutically acceptable salts" include the acid addition salts (formed with the free amino groups of the polypeptide) and which are formed with inorganic acids such as, for example, hydrochloric or phosphoric acids, or such organic acids as acetic, mandelic, oxalic, and tartaric. Salts formed with the free carboxyl groups can also be derived from inorganic bases such as, for example, sodium, potassium, ammonium, calcium, or ferric hydroxides, and such organic bases as isopropylamine, trimethylamine, 2-ethylamino ethanol, and histidine.

[0363] Compositions for oral administration can form solutions, suspensions, tablets, pills, capsules, sustained release formulations, oral rinses, or powders.

[0364] The term "unit dosage form," as used herein, refers to physically discrete units suitable as unitary dosages for human and animal subjects, each unit containing a predetermined quantity of compounds of the present invention calculated in an "effective amount," that is, a dosage sufficient to produce the desired result or effect in association with a pharmaceutically acceptable carrier. The specifications for the novel unit dosage forms of the present invention depend on the particular compound employed, the host, and the effect to be achieved, as well as the pharmacodynamics associated with each compound in the host.

#### **Compositions**

[0365] The present invention provides novel isolated polynucleotides encoding polypeptides and fragments thereof. The present invention also provides novel isolated polypeptides, fragments thereof, and compositions comprising same. The present invention further provides polynucleotide compositions that can be used to identify the polypeptides.

[0366] The present invention provides recombinant vectors and host cells for use in gene expression, primer pairs for use in hybridizations, computer-based embodiments for use in bioinformatics, and transgenic animals and embryonic stem cell lines for use in mutating and regulating gene expression.

#### **Nucleic Acids**

##### Sequences

[0367] This invention provides genes encoding proteins, the encoded proteins, and fragments and homologs thereof. It provides human polynucleotide sequences and the corresponding mouse polynucleotide sequences.

[0368] The nucleic acids of the subject invention can encode all or a part of the subject proteins. Double or single stranded fragments can be obtained from the DNA sequence by chemically synthesizing oligonucleotides in accordance with conventional methods, for example by restriction enzyme digestion or polymerase chain reaction (PCR) amplification. The use of the polymerase chain reaction has been described (Saiki et al., 1985) and current techniques have been reviewed (Sambrook et al., 1989; McPherson et al. 2000; Dieffenbach and Dveksler, 1995). For the most part, DNA fragments will be of at least about 5 nucleotides, at least about 8 nucleotides, at least about 10 nucleotides, at least about 15 nucleotides, at least about 18 nucleotides, at least about 20 nucleotides, at least about 25 nucleotides, at least about 30 nucleotides, or at least about 50 nucleotides, at least about 75 nucleotides, or at least about 100 nucleotides. Nucleic acid compositions that encode at least six contiguous amino acids (i.e., fragments of 18 nucleotides or more), for example, nucleic acid compositions encoding at least 8 contiguous amino acids (i.e., fragments of 24 nucleotides or more), are useful in directing the expression or the synthesis of peptides that can be used as immunogens (Lerner, 1982; Shinnick et al., 1983; Sutcliffe et al., 1983).

[0369] In some embodiments, a polynucleotide of the invention comprises a nucleotide sequence of at least about 5, at least about 8, at least about 10, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 50, at least about 75, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, at least about 600, at least about 650, at least about 700, at least about 750, at least about 800, at least about 850, at least about 900, at least about 950, at least about 1000, at least about 1100, at least about 1200, at least about 1300, at least about 1400, at least about 1500, at least about 1600, at least about 1700, at least about 1800, at least about 1900, at least about 2000, at least about 2100, at least about 2200, at least about 2300, at least about 2400, at least about 2500, at least about 3000, at least about 4000, or at least about 5000 contiguous nucleotides of any one of the sequences shown in SEQ ID NOS.: 1-104, or the coding region thereof, or a complement thereof.

[0370] In other embodiments, a polynucleotide of the invention has at least about 60%, 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or at least

about 99% nucleotide sequence identity with a nucleotide sequence, or a fragment thereof, of the coding region of any one of the sequences shown in SEQ ID NOS.: 1-104, or a complement thereof. These sequence variants include naturally-occurring variants (e.g., SNPs, allelic variants, and homologs from other species), degenerate variants, variants associated with disease or pathological states, and variants resulting from random or directed mutagenesis, as well as from chemical or other modification.

[0371] In some embodiments, a polynucleotide of the invention comprises a nucleotide sequence that encodes a polypeptide comprising an amino acid sequence of at least about 5, at least about 8, at least about 10, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 50, at least about 75, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, at least about 600, at least about 650, at least about 700, at least about 750, at least about 800, at least about 850, at least about 900, at least about 950, or at least about 1000 contiguous amino acids of at least one of the sequences encoded by SEQ ID NOS.: 1-104.

[0372] In some embodiment, the present invention includes the present polynucleotide selected from SEQ ID NOS.: 1 - 104, which contain 300 bp of 5' terminus of a protein encoding polynucleotide sequence. Such a polynucleotide is useful for the purposes of clustering gene sequences to determine gene family.

[0373] In further embodiments, a polynucleotide of the invention hybridizes under stringent hybridization conditions to a polynucleotide having the coding region of any one of the sequences shown in SEQ ID NOS.: 1 - 104, or a complement thereof.

[0374] The polynucleotides of the invention include those that encode variants of the polypeptide sequences encoded by the polynucleotides of the Sequence Listing. In some embodiments, these polynucleotides encode variant polypeptides that include insertions, additions, deletions, or substitutions compared with the polypeptides encoded by the nucleotide sequences shown in SEQ ID NOS.: 1 - 104, and in Table 1. Conservative amino acid substitutions include serine/threonine, valine/leucine/isoleucine, asparagine/histidine/glutamine, glutamic acid/aspartic acid, etc. (Gonnet et al., 1992).

[0375] The nucleic acids of the invention include degenerate variants that can be translated, according to the standard genetic code, to provide an amino acid

sequence identical to that translated from the nucleic acid sequences herein. For example, synonymous codons include GGG, GGA, GGC, and GGU, each encoding Glycine.

[0376] The nucleic acids of the invention include single nucleotide polymorphisms (SNPs), which occur frequently in eukaryotic genomes (Lander, et al. 2001). The nucleotide sequence determined from one individual of a species can differ from other allelic forms present within the population.

[0377] The nucleic acids of the invention include homologs of the polynucleotides. The source of homologous genes can be any species, e.g., primate species, particularly human; rodents, such as rats, hamsters, guinea pigs, and mice; rabbits, canines, felines; cattles, such as bovines, goats, pigs, sheep, equines, crustaceans, birds, chickens, reptiles, amphibians, fish, insects, plants, fungi, yeast, nematodes, etc. Among mammalian species, e.g., human and mouse, homologs have substantial sequence similarity, e.g., at least about 60% sequence identity, at least about 75% sequence identity, or at least about 80% sequence identity among nucleotide sequences. In many embodiments of interest, homology will be at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, or at least about 98%, where in certain embodiments of interest homology will be as high as about 99%.

[0378] Modifications in the native structure of nucleic acids, including alterations in the backbone, sugars or heterocyclic bases, have been shown to increase intracellular stability and binding affinity. Among useful changes in the backbone chemistry are phosphorothioates; phosphorodithioates, where both of the non-bridging oxygens are substituted with sulfur; phosphoramidites; alkyl phosphotriesters and boranophosphates. Achiral phosphate derivatives include 3'-O'-5'-S-phosphorothioate, 3'-S-5'-O-phosphorothioate, 3'-CH<sub>2</sub>-5'-O-phosphonate and 3'-NH-5'-O-phosphoroamidate. Peptide nucleic acids replace the entire ribose phosphodiester backbone with a peptide linkage.

[0379] Sugar modifications are also used to enhance stability and affinity. The  $\alpha$ -anomer of deoxyribose can be used, where the base is inverted with respect to the natural  $\beta$ -anomer. The 2'-OH of the ribose sugar can be altered to form 2'-O-methyl or 2'-O-allyl sugars, which provides resistance to degradation without comprising affinity.



[0380] Modification of the heterocyclic bases must maintain proper base pairing. Some useful substitutions include deoxyuridine for deoxythymidine; 5-methyl-2'-deoxycytidine and 5-bromo-2'-deoxycytidine for deoxycytidine. 5-propynyl-2'-deoxyuridine and 5-propynyl-2'-deoxycytidine have been shown to increase affinity and biological activity when substituted for deoxythymidine and deoxycytidine, respectively.

[0381] A genomic sequence of interest comprises the nucleic acid present between the initiation codon and the stop codon, as defined in the listed sequences, including all of the introns that are normally present in a native chromosome. It can further include the 3' and 5' untranslated regions found in the mature mRNA. It can further include specific transcriptional and translational regulatory sequences, such as promoters, enhancers, etc., including about 1 kb, about 2 kb, and possibly more, of flanking genomic DNA at either the 5' or 3' end of the transcribed region. The genomic DNA can be isolated as a fragment of 100 kbp or smaller; and substantially free of flanking chromosomal sequence. The genomic DNA flanking the coding region, either 3' or 5', or internal regulatory sequences as sometimes found in introns, contains sequences required for proper tissue and stage specific expression.

[0382] Nucleic acid molecules of the invention can comprise heterologous nucleic acid molecules, i.e., nucleic acid molecules other than the subject nucleic acid molecules, of any length. For example, the subject nucleic acid molecules can be flanked on the 5' and/or 3' ends by heterologous nucleic acid molecules of from about 1 nucleotide to about 10 nucleotides, from about 10 nucleotides to about 20 nucleotides, from about 20 nucleotides to about 50 nucleotides, from about 50 nucleotides to about 100 nucleotides, from about 100 nucleotides to about 250 nucleotides, from about 250 nucleotides to about 500 nucleotides, or from about 500 nucleotides to about 1000 nucleotides, or more in length.

[0383] The subject polynucleotides include those that encode fusion proteins comprising the subject polypeptides fused to "fusion partners." For example, the present soluble receptor or ligand can be fused to an immunoglobulin fragment, such as an Fc fragment for stability in circulation or to fix complement. Other polypeptide fragments that have equivalent capabilities as the Fc fragments can also be used herein.

[0384] The isolated nucleic acids of the invention can be used as probes to detect and characterize gross alteration in a genomic locus, such as deletions,

insertions, translocations, and duplications, e.g., applying fluorescence *in situ* hybridization (FISH) techniques to examine chromosome spreads (Andreeff et al., 1999). The nucleic acids are also useful for detecting smaller genomic alterations, such as deletions, insertions, additions, translocations, and substitutions (e.g., SNPs).

[0385] When used as probes to detect nucleic acid molecules capable of hybridizing with nucleic acids described in the Sequence Listing, the nucleic acid molecules can be flanked by heterologous sequences of any length. When used as probes, a subject nucleic acid can include nucleotide analogs that incorporate labels that are directly detectable, such as radiolabels or fluorophores, or nucleotide analogs that incorporate labels that can be visualized in a subsequent reaction, such as biotin or various haptens. Haptens that are commonly conjugated to nucleotides for subsequent labeling include biotin, digoxigenin, and dinitrophenyl.

[0386] Suitable fluorescent labels include fluorochromes e.g., fluorescein and its derivatives, e.g., fluorescein isothiocyanate (FITC-6-carboxyfluorescein (6-FAM), 2',7'-dimethoxy-4',5'-dichloro-6-carboxyfluorescein (JOE), ), 6-carboxy-2',4',7',4',7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM); coumarin and its derivatives, e.g., 7-amino-4-methylcoumarin, aminocoumarin; bodipy dyes, such as Bodipy FL; cascade blue; Oregon green; rhodamine dyes, e.g., rhodamine, 6-carboxy-X-rhodamine (ROX), Texas red, phycoerythrin, and tetramethylrhodamine; eosins and erythrosins; cyanine dyes, e.g., allophycocyanin, Cy3 and Cy5 or N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA); macrocyclic chelates of lanthanide ions, e.g., quantum dye, etc; and chemiluminescent molecules, e.g., luciferases.

[0387] Fluorescent labels also include a green fluorescent protein (GFP), i.e., a "humanized" version of a GFP, e.g., wherein codons of the naturally-occurring nucleotide sequence are changed to more closely match human codon bias; a GFP derived from *Aequoria victoria* or a derivative thereof, e.g., a "humanized" derivative such as Enhanced GFP, which are available commercially, e.g., from Clontech, Inc.; other fluorescent mutants of a GFP from *Aequoria victoria*, e.g., as described in U.S. Patent No. 6,066,476; 6,020,192; 5,985,577; 5,976,796; 5,968,750; 5,968,738; 5,958,713; 5,919,445; 5,874,304; a GFP from another species such as *Renilla reniformis*, *Renilla mulleri*, or *Ptilosarcus guernyi*, as previously described (WO 99/49019; Peelle et al., 2001), "humanized" recombinant GFP (hrGFP) (Stratagene®);

any of a variety of fluorescent and colored proteins from Anthozoan species, (e.g., Matz et al., 1999).

[0388] Probes can also contain fluorescent analogs, including commercially available fluorescent nucleotide analogs that can readily be incorporated into a subject nucleic acid. These include deoxyribonucleotides and/or ribonucleotide analogs labeled with Cy3, Cy5, Texas Red, Alexa Fluor dyes, rhodamine, cascade blue, or BODIPY, and the like.

[0389] Suitable radioactive labels include, e.g.,  $^{32}\text{P}$ ,  $^{35}\text{S}$ , or  $^3\text{H}$ . For example, probes can contain radiolabeled analogs, including those commonly labeled with  $^{32}\text{P}$  or  $^{35}\text{S}$ , such as  $\alpha$ - $^{32}\text{P}$ -dATP, -dTTP, -dCTP, and dGTP;  $\gamma$ - $^{35}\text{S}$ -GTP and  $\alpha$ - $^{35}\text{S}$ -dATP, and the like.

[0390] Nucleic acids of the invention can also be bound to a substrate. Subject nucleic acids can be attached covalently, attached to a surface of the support or applied to a derivatized surface in a chaotropic agent that facilitates denaturation and adherence, e.g., by noncovalent interactions, or some combination thereof. The nucleic acids can be bound to a substrate to which a plurality of other nucleic acids are concurrently bound, hybridization to each of the plurality of the bound nucleic acids being separately detectable.

[0391] The substrate can be porous or solid, planar or non-planar, unitary or distributed; and the bond between the nucleic acid and the substrate can be covalent or non-covalent. The substrate can be in the form of microbeads or nanobeads. Substrates include, but are not limited to, a membrane, such as nitrocellulose, nylon, positively-charged derivatized nylon; a solid substrate such as glass, amorphous silicon, crystalline silicon, plastics (including e.g., polymethylacrylic, polyethylene, polypropylene, polyacrylate, polymethylmethacrylate, polyvinylchloride, polytetrafluoroethylene, polystyrene, polycarbonate, polyacetal, polysulfone, cellulose acetate, or mixtures thereof).

[0392] The subject nucleic acids include antisense RNA, ribozymes, and RNAi. Further, The nucleic acids of the invention can be used for antisense or RNAi inhibition of transcription or translation using methods known in the art (Phillips, 1999a; Phillips, 1999b; Hartmann et al., 1999; Stein et al., 1998; Agrawal et al., 1998).

### *Expression Vectors*

[0393] The instant invention further provides host cells, e.g., recombinant host cells, that comprise a subject nucleic acid, host cells that comprise a recombinant vector, and host cells that secrete antibodies of the invention. Subject host cells can be cultured *in vitro*, or can be part of a multicellular organism. Host cells are described in more detail below. The instant invention further provides transgenic plants and non-human animals, as described in more detail below.

[0394] In addition to the plurality of uses described in greater detail in following sections, the subject nucleic acids find use in the preparation of all or a portion of the polypeptides of the subject invention, as described above, using an expression system. For expression, an expression vector can be employed. The expression vector will provide a transcriptional and translational initiation region, which may be inducible, conditionally-active, or constitutive, or tissue-specific, where the coding region is operably linked under the transcriptional control of the transcriptional initiation region, and a transcriptional and translational termination region. These control regions can be native to a gene encoding the subject peptides, or can be derived from heterologous or exogenous sources.

[0395] The subject nucleic acids can also be provided as part of a vector (e.g., a polynucleotide construct comprising an expression cassette), a wide variety of which are known in the art. Vectors include, but are not limited to, plasmids; cosmids; viral vectors; human, yeast, bacterial, P1-derived artificial chromosomes (HAC's, YAC's, BAC's, PAC's, etc.), mini-chromosomes, and the like. Vectors are amply described in numerous publications well known to those in the art (Ausubel, et al.; Jones et al., 1998a; Jones et al., 1998b). Vectors can provide for nucleic acid expression, for nucleic acid propagation, or both.

[0396] A recombinant vector or construct that includes a nucleic acid of the invention is useful for propagating a nucleic acid in a host cell; such vectors are known as "cloning vectors." Vectors can transfer nucleic acid between host cells derived from disparate organisms; these are known in the art as "shuttle vectors." Vectors can also insert a subject nucleic acid into a host cell's chromosome; these are known in the art as "insertion vectors." Vectors can express either sense or antisense RNA transcripts of the invention *in vitro* (e.g., in a cell-free system or within an *in vitro* cultured host cell) or *in vivo* (e.g., in a multicellular plant or animal); these are

known in the art as "expression vectors," which can be part of an expression system. Expression vectors can also produce a subject antibody.

[0397] Vectors typically include at least one origin of replication, at least one site for insertion of heterologous nucleic acid (e.g., in the form of a polylinker with multiple, tightly clustered, single cutting restriction endonuclease recognition sites), and at least one selectable marker, although some integrative vectors will lack an origin that is functional in the host to be chromosomally modified, and some vectors will lack selectable markers. Vectors are transiently or stably maintained in the cells, usually for a period of at least about one day, at least about several days to at least about several weeks.

[0398] Prior to vector insertion, the DNA of interest will be obtained substantially free of other nucleic acid sequences. The DNA can be "recombinant," and flanked by one or more nucleotides with which it is not normally associated on a naturally occurring chromosome.

[0399] Expression vectors generally have convenient restriction sites located near the promoter sequence to provide for the insertion of nucleic acid sequences encoding heterologous protein or RNA molecules. A selectable marker operative in the expression system or host can be present. Expression vectors can be used for the production of fusion proteins, where the fusion peptide provides additional functionality, i.e., increased protein synthesis, a leader sequence for secretion, stability, reactivity with defined antisera, or an enzyme marker, e.g.,  $\beta$ -galactosidase.

[0400] Promoters of the invention can be naturally contiguous or not naturally contiguous to the expressed nucleic acid molecule, to the nucleic acid molecule. Promoter can be inducible, a conditionally-active (such as the cre-lox promoter), constitutive, and/or tissue-specific.

[0401] Expression vectors can be prepared comprising a transcription cassette comprising a transcription initiation region, the gene or fragment thereof, and a transcriptional termination region. Of particular interest is the use of DNA sequences that allow for the expression of functional epitopes or domains, at least about 5, at least about 8, at least about 10, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 50, at least about 75, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at

least about 550, at least about 600, at least about 650, at least about 700, at least about 750, at least about 800, at least about 850, at least about 900, at least about 950, or at least about 1000 amino acids in length, or any of the above-described fragments, up to and including the complete open reading frame of the gene. After introduction of these DNA sequences, the cells containing the vector construct can be selected by means of a selectable marker, and the selected cells expanded and used as expression-competent host cells.

[0402] Host cells can comprise prokaryotes or eukaryotes that express proteins and polypeptides in accordance with conventional methods, the method depending on the purpose for expression. For large scale production of the protein, a unicellular organism, such as *E. coli*, *B. subtilis*, *S. cerevisiae*, insect cells in combination with baculovirus vectors, or cells of a higher organism such as vertebrates, particularly mammals, e.g., COS 7 cells, can be used as the expression host cells. In some situations, it is desirable to express eukaryotic genes in eukaryotic cells, where the encoded protein will benefit from native folding and post-translational modifications.

[0403] Specific expression systems of interest include plants, bacteria, yeast, insect cells, and mammalian cell-derived expression systems. Representative systems from each of these categories are provided below.

[0404] Expression systems in plants include those described in U.S. Patent No. 6,096,546 and U.S. Patent No. 6,127,145.

[0405] Expression systems in bacteria include those described by Chang et al., 1978; Goeddel et al., 1979; Goeddel et al., 1980; EP 0 036,776; U.S. Patent No. 4,551,433; DeBoer et al., 1983; and Siebenlist et al., 1980.

[0406] Expression systems in yeast include those described by Hinnen et al., 1978; Ito et al., 1983; Kurtz et al., 1986; Kunze et al., 1985; Gleeson et al., 1986; Roggenkamp et al., 1986; Das et al., 1984; De Louvencourt et al., 1983; Van den Berg et al., 1990; Kunze et al., 1985; Cregg et al., 1985; U.S. Patent Nos. 4,837,148 and 4,929,555; Beach and Nurse, 1981; Davidow et al., 1985; Gaillardin et al., 1985; Ballance et al., 1983; Tilburn et al., 1983; Yelton et al., 1984; Kelly and Hynes, 1985; EP 0 244,234; WO 91/00357; and U.S. Patent No. 6,080,559.

[0407] Expression systems for heterologous genes in insects include those described in U.S. Patent No. 4,745,051; Friesen et al., 1986; EP 0 127,839; EP 0 155,476; Vlak et al., 1988; Miller et al., 1988; Carbonell et al., 1988; Maeda et al.,

1985; Lebacqz-Verheyden et al., 1988; Smith et al., 1985); Miyajima et al., 1987; and Martin et al., 1988. Numerous baculoviral strains and variants and corresponding permissive insect host cells are described in Luckow et al., 1988, Miller et al., 1986, and Maeda et al., 1985. The insect cell expression system is useful not only for production of heterologous proteins intracellularly, but can be used for expression of transmembrane proteins on the insect cell surfaces. Such insect cells can be used as immunogen for production of antibodies, for example, by injection of the insect cells into mice or rabbits or other suitable animals, for production of antibodies.

[0408] Mammalian expression systems include those described in Dijkema et al., 1985; Gorman et al., 1982; Boshart et al., 1985; and U.S. Patent No. 4,399,216. Additional features of mammalian expression are facilitated as described in Ham and Wallace, 1979; Barnes and Sato, 1980 U.S. Patent Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, WO 90/103430, WO 87/00195, and U.S. RE 30,985. Mammalian cell expression systems can also be used for production of antibodies.

[0409] The present polynucleotides can also be used in cell-free expression systems such as bacterial system, e.g., *E. coli* lysate, rabbit reticulocyte lysate system, wheat germ extract system, frog oocyte lysate system, and the like which is conventional in the art. See, for example, WO 00/68412, WO 01/27260, WO 02/24939, WO 02/38790, WO 91/02076, and WO 91/02075.

[0410] When any of the above-referenced host cells, or other appropriate host cells or organisms, are used to replicate and/or express the polynucleotides of the invention, the resulting replicated nucleic acid, RNA, expressed protein or polypeptide, is within the scope of the invention as a product of the host cell or organism.

[0411] Once the gene corresponding to a selected polynucleotide is identified, its expression can be regulated in the gene's native cell types. For example, an endogenous gene of a cell can be regulated by an exogenous regulatory sequence inserted into the genome of the cell at a location that will enhance or reduce expression of the gene corresponding to the subject polypeptide. The regulatory sequence can be designed to integrate into the genome via homologous recombination, as disclosed in U.S. Patent Nos. 5,641,670 and 5,733,761, the disclosures of which are herein incorporated by reference. Alternatively, it can be designed to integrate into the genome via non-homologous recombination, as described in WO 99/15650, the disclosure of which is also herein incorporated by

reference. Also encompassed in the subject invention is the production of proteins without manipulating the encoding nucleic acid itself, but rather by integrating a regulatory sequence into the genome of a cell that already includes a gene that encodes the protein of interest; this production method is described in the above-incorporated patent documents.

#### *Isolated Primer Pairs*

[0412] In some embodiments, the invention provides isolated nucleic acids that, when used as primers in a polymerase chain reaction, amplify a subject polynucleotide, or a polynucleotide containing a subject polynucleotide. The amplified polynucleotide is from about 20 to about 50, from about 50 to about 75, from about 75 to about 100, from about 100 to about 125, from about 125 to about 150, from about 150 to about 175, from about 175 to about 200, from about 200 to about 250, from about 250 to about 300, from about 300 to about 350, from about 350 to about 400, from about 400 to about 500, from about 500 to about 600, from about 600 to about 700, from about 700 to about 800, from about 800 to about 900, from about 900 to about 1000, from about 1000 to about 2000, from about 2000 to about 3000, from about 3000 to about 4000, from about 4000 to about 5000, or from about 5000 to about 6000 nucleotides or more in length.

[0413] The isolated nucleic acids themselves are from about 10 to about 20, from about 20 to about 30, from about 30 to about 40, from about 40 to about 50, from about 50 to about 100, or from about 100 to about 200 nucleotides in length. Generally, the nucleic acids are used in pairs in a polymerase chain reaction, where they are referred to as "forward" and "reverse" primers.

[0414] Thus, in some embodiments, the invention provides a pair of isolated nucleic acid molecules, each from about 10 to about 200 nucleotides in length, the first nucleic acid molecule of the pair comprising a sequence of at least 10 contiguous nucleotides having 100% sequence identity to a nucleic acid sequence as shown in SEQ ID NOS.: 1 - 104 and the second nucleic acid molecule of the pair comprising a sequence of at least 10 contiguous nucleotides having 100% sequence identity to the reverse complement of the nucleic acid sequence shown in SEQ ID NOS.: 1 - 104, wherein the sequence of the second nucleic acid molecule is located 3' of the nucleic acid sequence of the first nucleic acid molecule shown in SEQ ID NOS.: 1 - 104. The primer nucleic acids are prepared using any known method, e.g., automated synthesis,



and can be chosen to specifically amplify a cDNA copy of an mRNA encoding a subject polypeptide.

[0415] In some embodiments, the first and/or the second nucleic acid molecules comprise a detectable label. The label can be a radioactive molecule, fluorescent molecule or another molecule, e.g., hapten, as described in detail above. Further, the label can be a two stage system, where the amplified DNA is conjugated to another molecule, i.e., biotin, digoxin, or a hapten, that has a high affinity binding partner, i.e., avidin, antidigoxin, or a specific antibody, respectively, and the binding partner conjugated to a detectable label. The label can be conjugated to one or both of the primers. Alternatively, the pool of nucleotides used in the amplification is labeled, so as to incorporate the label into the amplification product.

[0416] Conditions that increase stringency of both DNA/DNA and DNA/RNA hybridization reactions are widely known and published in the art. See, for example, Sambrook, 1989, and examples provided above. Examples of relevant conditions include (in order of increasing stringency): incubation temperatures of 25°C, 37°C, 50°C, and 68°C; buffer concentrations of 10 x SSC, 6 x SSC, 1 x SSC, 0.1 x SSC (where 1 x SSC is 0.15 M NaCl and 15 mM citrate buffer); and their equivalents using other buffer systems; formamide concentrations of 0%, 25%, 50%, and 75%; incubation times from 5 minutes to 24 hours; 1, 2, or more washing steps; wash incubation times of 1, 2, or 15 minutes; and wash solutions of 6 x SSC, 1 x SSC, 0.1 x SSC, or deionized water.

[0417] For example, "high stringency conditions" include hybridization in 50% formamide, 5X SSC, 0.2 µg/µl poly(dA), 0.2 µg/µl human cot1 DNA, and 0.5% SDS, in a humid oven at 42°C overnight, followed by successive washes in 1X SSC, 0.2% SDS at 55°C for 5 minutes, followed by washing at 0.1X SSC, 0.2% SDS at 55°C for 20 minutes. Further examples of high stringency conditions include hybridization at 50°C and 0.1×SSC (15 mM sodium chloride/1.5 mM sodium citrate); overnight incubation at 42°C in a solution containing 50% formamide, 1 × SSC (150 mM NaCl, 15 mM sodium citrate), 50 mM sodium phosphate (pH 7.6), 5 × Denhardt's solution, 10% dextran sulfate, and 20 µg/ml denatured, sheared salmon sperm DNA, followed by washing the filters in 0.1 × SSC at about 65°. High stringency conditions also include aqueous hybridization (e.g., free of formamide) in 6X SSC (where 20X SSC contains 3.0 M NaCl and 0.3 M sodium citrate), 1% sodium

dodecyl sulfate (SDS) at 65°C for about 8 hours (or more), followed by one or more washes in 0.2 X SSC, 0.1% SDS at 65°C. Highly stringent hybridization conditions are hybridization conditions that are at least as stringent as any one of the above representative conditions. Other stringent hybridization conditions are known in the art and can also be employed to identify nucleic acids of this particular embodiment of the invention.

[0418] Conditions of "reduced stringency," suitable for hybridization to molecules encoding structurally and functionally related proteins, or otherwise serving related or associated functions, are the same as those for high stringency conditions but with a reduction in temperature for hybridization and washing to lower temperatures (e.g., room temperature or about 22°C to 25°C). For example, moderate stringency conditions include aqueous hybridization (e.g., free of formamide) in 6X SSC, 1% SDS at 65°C for about 8 hours (or more), followed by one or more washes in 2X SSC, 0.1% SDS at room temperature. Low stringency conditions include, for example, aqueous hybridization at 50°C and 6×SSC (0.9 M sodium chloride/0.09 M sodium citrate) and washing at 25°C in 1×SSC (0.15 M sodium chloride/0.015 M sodium citrate).

[0419] The specificity of a hybridization reaction allows any single-stranded sequence of nucleotides to be labeled with a radioisotope or chemical and used as a probe to find a complementary strand, even in a cell or cell extract that contains millions of different DNA and RNA sequences. Probes of this type are widely used to detect the nucleic acids corresponding to specific genes, both to facilitate the purification and characterization of the genes after cell lysis and to localize them in cells, tissues, and organisms.

[0420] Moreover, by carrying out hybridization reactions under conditions of "reduced stringency," a probe prepared from one gene can be used to find homologous evolutionary relatives - both in the same organism, where the relatives form part of a gene family, and in other organisms, where the evolutionary history of the nucleotide sequence can be traced. A person skilled in the art would recognize how to modify the conditions to achieve the requisite degree of stringency for a particular hybridization.

### *Libraries*

[0421] The polynucleotide libraries of the invention generally comprise a collection of sequence information of a plurality of polynucleotide sequences, where at least one of the polynucleotides has a sequence shown in SEQ ID NOS.: 1 - 104. By plurality is meant at least 2, at least 3, or at least all of the sequences in the Sequence Listing. The information may be provided in either biochemical form (e.g., as a collection of polynucleotide molecules), or in electronic form (e.g., as a collection of polynucleotide sequences stored in a computer-readable form, as in a computer-based system, a computer data file, and/or as a part of a computer program). The length and number of polynucleotides in the library will vary with the nature of the library, e.g., if the library is an oligonucleotide array, a cDNA array, or a computer database of the sequence information.

[0422] The sequence information contained in either a biochemical or an electronic library of polynucleotides can be used in a variety of ways, e.g., as a resource for gene discovery, as a representation of sequences expressed in a selected cell type (e.g., cell type markers), or as markers of a given disorder or disease state. In general, a disease marker is a representation of a gene product that is present in all cells affected by disease either at an increased or decreased level relative to a normal cell (e.g., a cell of the same or similar type that is not substantially affected by disease). For example, a polynucleotide sequence in a library can be a polynucleotide that represents an mRNA, polypeptide, or other gene product encoded by the polynucleotide, that is either over-expressed or under-expressed in one cell compared to another (e.g., a first cell type compared to a second cell type; a normal cell compared to a diseased cell; a cell not exposed to a signal or stimulus compared to a cell exposed to that signal or stimulus; and the like).

[0423] The nucleotide sequence information of the library can be embodied in any suitable form, e.g., electronic or biochemical forms. For example, a library of sequence information embodied in electronic form comprises an accessible computer data file that may contain the representative nucleotide sequences of genes that are differentially expressed (e.g., over-expressed or under-expressed) as between, e.g., a first cell type compared to a second cell type (e.g., expression in a brain cell compared to expression in a kidney cell); a normal cell compared to a diseased cell (e.g., a non-cancerous cell compared to a cancerous cell); a cell not exposed to an internal or external signal or stimulus compared to a cell exposed to that signal or stimulus (e.g.,

a cell contacted with a ligand compared to a control cell not contacted with the ligand); and the like. Other combinations and comparisons of cells will be readily apparent to the ordinarily skilled artisan. Biochemical embodiments of the library include a collection of nucleic acid molecules that have the sequences of the genes in the library, where the nucleic acids can correspond to the entire gene in the library or to a fragment thereof, as described in greater detail below.

[0424] Where the library is an electronic library, the nucleic acid sequence information can be present in a variety of media. For example, the nucleic acid sequences of any of the polynucleotides shown in SEQ ID NOS.: 1 - 104 can be recorded on computer readable media of a computer-based system, e.g., any medium that can be read and accessed directly by a computer. One of skill in the art can readily appreciate how any of the presently known computer readable mediums can be used to create a manufacture comprising a recording of the present sequence information. Any convenient data storage structure can be chosen, based on the means used to access the stored information. A variety of data processor programs and formats can be used for storage, e.g., word processing text file, database format, etc. In addition to the sequence information, electronic versions of the libraries of the invention can be provided in conjunction or connection with other computer-readable information and/or other types of computer-based files (e.g., searchable files, executable files, etc, including, but not limited to, for example, search program software, etc.).

[0425] By providing the nucleotide sequence in computer readable form in a computer-based system, the information can be accessed for a variety of purposes. Computer software to access sequence information is publicly available. Conventional bioinformatics tools can be utilized to analyze sequences to determine sequence identity, sequence similarity, and gap information. For example, the gapped BLAST (Altschul et al., 1990, Altschul et al., 1997), and BLAZE (Brutlag et al., 1993) search algorithms on a Sybase system, or the TeraBLAST (TimeLogic, Crystal Bay, Nevada) program optionally running on a specialized computer platform available from TimeLogic, can be used to identify open reading frames (ORFs) within the genome that contain homology to ORFs from other organisms. Homology between sequences of interest can be determined using the local homology algorithm of Smith and Waterman, 1981, as well as the BestFit program (Rechid et al., 1989), and the FastDB algorithm (FastDB, 1988; described in Current Methods in Sequence

Comparison and Analysis, Macromolecule Sequencing and Synthesis, Selected Methods and Applications, pp. 127-149, 1988, Alan R. Liss, Inc).

[0426] Alignment programs that permit gaps in the sequence include Clustalw (Thompson et al., 1994), FASTA3 (Pearson, 2000) Align0 (Myers and Miller, 1988), and TCOFFEE (Notredame et al., 2000). Other methods for comparing and aligning nucleotide and protein sequences include, for example, BLASTX (NCBI), the Wise package (Birney and Durbin, 2000), and FASTX (Pearson, 2000). These algorithms determine sequence homology between nucleotide and protein sequences without translating the nucleotide sequences into protein sequences. Other techniques for alignment are also known in the art (Doolittle, et al., 1996; BLAST, available from the National Center for Biotechnology Information; FASTA, available in the Genetics Computing Group (GCG) package, from Madison, Wisconsin, USA, a wholly owned subsidiary of Oxford Molecular Group, Inc.; Schlessinger, 1988a; Schlessinger, 1988b; and Needleman and Wunch, 1970).

[0427] Sequence similarity is calculated based on a reference sequence, which may be a subset of a larger sequence, such as a conserved motif, coding region, flanking region, etc. The reference sequence is usually at least about 18 nt long, at least about 30 nt long, or may extend to the complete sequence that is being compared.

[0428] One parameter for determining percent sequence identity is the percentage of the alignment in the region of strongest alignment between a target and a query sequence. Methods for determining this percentage involve, for example, counting the number of aligned bases of a query sequence in the region of strongest alignment and dividing this number by the total number of bases in the region. For example, 10 matches divided by 11 total residues gives a percent sequence identity of approximately 90.9%. The length of the aligned region is typically at least about 55%, at least about 58%, or at least about 60% of the total sequence length, and can be as great as about 62%, as great as about 64%, and even as great as about 66% of the total sequence length.

[0429] The present invention includes human and mouse polynucleotide and polypeptide sequences that are at least about 95%, at least about 96%, at least about 97%, at least about 98%, or at least about 99% homologous to the sequences in the Sequence Listing, based on using the method of determining sequence identity with the insertion of gaps to detect the maximum degree of sequence identity. In other

embodiments of interest, homology will be at least about 80%, at least about 85%, or as high as about 90%.

[0430] A variety of structural formats for the input and output means can be used to input and output the information in the computer-based systems of the present invention. One format for an output means ranks the relative expression levels of different polynucleotides. Such presentation provides a skilled artisan with a ranking of relative expression levels to determine a gene expression profile.

[0431] As discussed above, the library of the invention also encompasses biochemical libraries of the polynucleotides shown in SEQ ID NOS.: 1 - 104 and 2463 - 3697, e.g., collections of nucleic acids representing the provided polynucleotides. The biochemical libraries can take a variety of forms, e.g., a solution of cDNAs, a pattern of probe nucleic acids stably associated with a surface of a solid support (i.e., an array) and the like. Of particular interest are nucleic acid arrays in which one or more of the polynucleotide sequences shown in SEQ ID NOS.: 1 - 104 is represented on the array. A variety of different array formats have been developed and are known to those of skill in the art. The arrays of the subject invention find use in a variety of applications, including gene expression analysis, drug screening, mutation analysis, and the like, as disclosed in the herein-listed exemplary patent documents.

[0432] In addition to the above nucleic acid libraries, analogous libraries of polypeptides are also provided, where the polypeptides of the library will represent at least a portion of the polypeptides encoded by a gene corresponding to one or more of the sequences shown in SEQ ID NOS.: 1 - 104.

[0433] Further, analogous libraries of antibodies are also provided, where the libraries comprise antibodies or fragments thereof that specifically bind to at least a portion of at least one of the subject polypeptides. Further, antibody libraries may comprise antibodies or fragments thereof that specifically inhibit binding of a subject polypeptide to its ligand or substrate, or that specifically inhibit binding of a subject polypeptide as a substrate to another molecule. Moreover, corresponding nucleic acid libraries are also provided, comprising polynucleotide sequences that encode the antibodies or antibody fragments described above.

## Polypeptides

### Sequences

[0434] This invention provides novel polypeptides, and related polypeptide compositions. The novel polypeptides of the invention encompass proteins encoded by the nucleic acids having nucleotide sequences shown in SEQ ID NOS.: 1 - 104. The subject polypeptides are human polypeptides, fragments thereof, variants (such as splice variants), homologs from other species, and derivatives thereof. In particular embodiments, a polypeptide of the invention has an amino acid sequence substantially identical to the sequence of any polypeptide encoded by a polynucleotide sequence shown in SEQ ID NOS.: 1 - 104.

[0435] These polypeptides may reside within the cell, or extracellularly. They may be secreted from the cell, reside in the cytoplasm, in the membranes, or in any of the intracellular organelles, including the nucleus, mitochondria, ribosomes, or storage granules.

[0436] In many embodiments, a novel polypeptide of the invention functions as a secreted protein, a single-transmembrane protein, a multiple-transmembrane protein, a kinase, a protein kinase, a ligase, a nuclear hormone receptor, a phosphatase, a protease, a phosphodiesterase, a kinesin, an immunoglobulin, a T-cell receptor, or a glycosylphosphatidylinositol anchor. A novel polypeptide of the invention can also possess one or more of the following functions or properties: (1) an activator functioning to regulate one or more genes by increasing the rate of transcription, (2) an activator functioning to positively modulate an allosteric enzyme, (3) an adaptor functioning to sort cargo molecules into transport vesicles, (4) an adaptor functioning to form a clathrin-coated vesicle, (5) an adhesion molecule functioning to mediate the adhesion of cells with other cells and/or the extracellular matrix, (6) an ATPase functioning to move ions or small molecules across a membrane against a chemical concentration gradient or electrical potential, (7) an ATPase functioning to translocate nucleotides across membranes, (8) a breakpoint-related sequence functioning as an oncoprotein, (9) a breakpoint-related sequence functioning as a tumor-specific antigen, (10) a channel functioning as a water channel, (11) a channel functioning as an ion channel, (12) a checkpoint-related sequence functioning at DNA damage checkpoints, (13) a checkpoint-related sequence functioning at replication checkpoints, (14) a checkpoint-related sequence functioning to initiate signal transduction cascades eliciting cell cycle arrest, DNA repair, or

apoptosis, (15) a complex functioning as a protein scaffold, (16) a complex functioning in ADP-ribosylation, (17) a dehydrogenase functioning to synthesize amino acids, (18) a disintegrin functioning to inhibit blood clotting, (19) a disintegrin functioning as a metallopeptidase, (20) a GTPase functioning as a negative regulator of p53, (21) a GTPase functioning to stimulate ras GTPase activity, (22) a helicase functioning in DNA replication, (23) a hydrolase functioning in propionate metabolism, (24) an integrase functioning to integrate a DNA copy of a retroviral genome into a host chromosome, (25) an integrin functioning as a tumor marker, (26) an integrin functioning in cell migration, (27) an isomerase functioning as an immunosuppressant, (28) a membrane protein functioning as a scaffolding component at the cytoplasmic face of a lipid raft, (29) a membrane protein functioning as a ligand for a receptor tyrosine kinase, (30) oxygenases and peroxidases functioning as antioxidants, (31) a phospholipase functioning in eicosanoid synthesis, (32) a phospholipase functioning in preserving the intestinal mucosa, (33) a prosaposin functioning in lipid catabolism, (34) a proteasome component functioning in muscle wasting, (35) a reductase-related sequence functioning as a coenzyme A reductase inhibitor, (36) a reverse transcriptase functioning as an RNA-dependent reverse transcriptase, (37) a reverse transcriptase functioning as a DNA-dependent reverse transcriptase, (38) an RNase functioning in viral assembly, (39) an RNase H functioning to form oligonucleotides that prime DNA synthesis, (40) an RNase H functioning to cleave the RNA strand of an RNA-DNA hybrid, (41) SH3 domains functioning in actin cytoskeletal organization, (42) SH3 domains functioning in signal transduction, (43) a synthetase functioning as an autoantigen (44) synthetases functioning in nucleotide sugar phosphate synthesis, (45) TATA boxes functioning as a transcription initiators, (46) tat functioning as a transcriptional coactivator, (47) transferases functioning in signal transduction, (48) transposases functioning as gene transfer agents, (49) ubiquitins functioning to protect cells against tumor necrosis factor induced cell death, (50) proteasome components and ubiquitin functioning in protein degradation, (51) a virus-related sequence functioning to confer resistance to infection by viruses, (52) other sequences of the invention interacting with one or more proteins, (53) other sequences of the invention enzymatically modifying one or more proteins, (54) other sequences of the invention binding one or more small molecule ligands, (55) other sequences of the invention binding one or more peptides,



(56) other sequences of the invention binding one or more carbohydrates, and (57) other sequences of the invention functioning in vesicular transport.

[0437] In some embodiments, the present novel polypeptide modulates the cells or tissues of animals, particularly humans, such as, for example, by stimulating, enhancing or inhibiting T or B cell function or the function of other hematopoietic cells or bone marrow cells; modulates adult or embryonic stem cell or precursor cell growth or differentiation; modulates cell function or activity of neuronal cells or other cells of the CNS, heart cells, liver cells, kidney cells, lung cells, pancreatic cells, gastrointestinal cells, spleen cells, breast cells, prostate cells, ovarian cells, and the like.

[0438] In some embodiments, a subject polypeptide is present as a multimer. Multimers include homodimers, homotrimers, homotetramers, and multimers that include more than four monomeric units. Multimers also include heteromultimers, e.g., heterodimers, heterotrimers, heterotetramers, etc. where the subject polypeptide is present in a complex with proteins other than the subject polypeptide. Where the multimer is a heteromultimer, the subject polypeptide can be present in a 1:1 ratio, a 1:2 ratio, a 2:1 ratio, or other ratio, with the other protein(s).

[0439] In addition to the above specifically listed proteins, polypeptides from other species are also provided, including mammals, such as: primates, rodents, e.g., mice, rats, hamsters, guinea pigs; domestic animals, e.g., sheep, pig, horse, cow, goat, rabbit, dog, cat; and humans, as well as non-mammalian species, e.g., avian, reptile and amphibian, insect, crustacean, fish, plant, fungus, and protozoa.

[0440] By "homolog" is meant a protein having at least about 35 %, at least about 40%, at least about 60%, at least about 70%, at least about 75%, at least about 80%, at least about 85%, at least about 90%, or at least about 95%, or higher, amino acid sequence identity to the reference polypeptide, as measured with the "GAP" program (part of the Wisconsin Sequence Analysis Package available through the Genetics Computer Group, Inc. (Madison WI)), where the parameters are: Gap weight:12; length weight:4. In many embodiments of interest, homology will be at least about 75%, at least about 80%, or at least 85%, where in certain embodiments of interest, homology will be as high as about 90%.

[0441] Also provided are polypeptides that are substantially identical to the at least one amino acid sequence shown in the Sequence Listing, or a fragment thereof, whereby substantially identical is meant that the protein has an amino acid

sequence identity to the reference sequence of at least about 75%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 97%, at least about 98%, or at least about 99%.

[0442] The proteins of the subject invention (e.g., polypeptides encoded by the nucleotide sequences shown in SEQ ID NOS.: 1 - 104 have been separated from their naturally occurring environment and are present in a non-naturally occurring environment. In certain embodiments, the proteins are present in a composition where they are more concentrated than in their naturally occurring environment. For example, purified polypeptides are provided.

[0443] In addition to naturally occurring proteins, polypeptides that vary from naturally occurring forms are also provided. Fusion proteins can comprise a subject polypeptide, or fragment thereof, and a polypeptide other than a subject polypeptide ("the fusion partner") fused in-frame at the N-terminus and/or C-terminus of the subject polypeptide, or internally to the subject polypeptide.

[0444] Suitable fusion partners include, but are not limited to, immunologically detectable proteins (e.g., epitope tags, such as hemagglutinin, FLAG, and c-myc); polypeptides that provide a detectable signal or that serve as detectable markers (e.g., a fluorescent protein, e.g., a green fluorescent protein, a fluorescent protein from an Anthozoan species;  $\beta$ -galactosidase; luciferase; cre recombinase; and the like); polypeptides that provide a catalytic function or induce a cellular response; polypeptides that provide for secretion of the fusion protein from a eukaryotic cell; polypeptides that provide for secretion of the fusion protein from a prokaryotic cell; polypeptides that provide for binding to metal ions (e.g., His<sub>n</sub>, where n = 3-10, e.g., 6His) and structural proteins. Fusion partners can also be those that are able to stabilize the present polypeptide, such as polyethylene glycol ("PEG") and a fragment of an immunoglobulin, such as the Fc fragment of IgG, IgE, IgA, IgM, and/or IgD.

[0445] Detection methods are chosen based on the detectable fusion partner. For example, where the fusion partner provides an immunologically recognizable epitope, an epitope-specific antibody can be used to quantitatively detect the level of polypeptide. In some embodiments, the fusion partner provides a detectable signal, and in these embodiments, the detection method is chosen based on the type of signal generated by the fusion partner. For example, where the fusion partner is a fluorescent protein, fluorescence is measured.

[0446] Where the fusion partner is an enzyme that yields a detectable product, the product can be detected using an appropriate means. For example,  $\beta$ -galactosidase can, depending on the substrate, yield a colored product that can be detected with a spectrophotometer, and the fluorescent protein luciferase can yield a luminescent product detectable with a luminometer.

[0447] In some embodiments, a polypeptide of the invention comprises at least about 5, at least about 8, at least about 10, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 50, at least about 75, at least about 100, at least about 150, at least about 200, at least about 250, at least about 300, at least about 350, at least about 400, at least about 450, at least about 500, at least about 550, at least about 600, at least about 650, at least about 700, at least about 750, at least about 800, at least about 850, at least about 900, at least about 950, or at least about 1000 contiguous amino acid residues of at least one of the sequences according to SEQ ID NOS.: 1 - 104, up to and including the entire amino acid sequence.

[0448] Fragments of the subject polypeptides, as well as polypeptides comprising such fragments, are also provided. Fragments of polypeptides of interest will typically be at least about 5, at least about 8, at least about 10, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, at least about 50, at least about 75, at least about 100, at least about 150, at least about 200, at least about 250, or at least 300 aa in length or longer, where the fragment will have a stretch of amino acids that is identical to the subject protein of at least about 5, at least about 8, at least about 10, at least about 15, at least about 18, at least about 20, at least about 25, at least about 30, or at least about 50 aa in length.

[0449] In some embodiments, fragments exhibit one or more activities associated with a corresponding naturally occurring polypeptide. Fragments find utility in generating antibodies to the full-length polypeptide; and in methods of screening for candidate agents that bind to and/or modulate polypeptide activity. Specific fragments of interest include those with enzymatic activity, those with biological activity including the ability to serve as an epitope or immunogen, and fragments that bind to other proteins or to nucleic acids.

[0450] The invention provides polypeptides comprising such fragments, including, e.g., fusion polypeptides comprising a subject polypeptide fragment fused in frame (directly or indirectly) to another protein (the "fusion partner"), such as the

signal peptide of one protein being fused to the mature polypeptide of another protein. Such fusion proteins are typically made by linking the encoding polynucleotides together in a vector or cassette. Suitable fusion partners include, but are not limited to, immunologically detectable proteins (e.g., epitope tags, such as hemagglutinin, FLAG, and c-myc); polypeptides that provide a detectable signal or that serve as detectable markers (e.g., a fluorescent protein, e.g., a green fluorescent protein, a fluorescent protein from an Anthozoan species;  $\beta$ -galactosidase; luciferase; cre recombinase); polypeptides that provide a catalytic function or induce a cellular response; polypeptides that provide for secretion of the fusion protein from a eukaryotic cell; polypeptides that provide for secretion of the fusion protein from a prokaryotic cell; polypeptides that provide for binding to metal ions (e.g., His<sub>n</sub>, where n = 3-10, e.g., 6His) and structural proteins. Fusion partners can also be those that are able to stabilize the present polypeptide, such as polyethylene glycol ("PEG") and a fragment of an immunoglobulin, such as the Fc fragment of IgG, IgE, IgA, IgM, and/or IgD.

#### *Polypeptide Preparation.*

[0451] Polypeptides of the invention can be obtained from naturally-occurring sources or produced synthetically. The sources of naturally occurring polypeptides will generally depend on the species from which the protein is to be derived, i.e., the proteins will be derived from biological sources that express the proteins. The subject proteins can also be derived from synthetic means, e.g., by expressing a recombinant gene encoding a protein of interest in a suitable system or host or enhancing endogenous expression, as described in more detail above. Further, small peptides can be synthesized in the laboratory by techniques well known in the art.

[0452] In all cases, the product can be recovered by any appropriate means known in the art. For example, convenient protein purification procedures can be employed (e.g., see Guide to Protein Purification, Deutscher et al., 1990). That is, a lysate can be prepared from the original source, (e.g., a cell expressing endogenous polypeptide, or a cell comprising the expression vector expressing the polypeptide(s)), and purified using HPLC, exclusion chromatography, gel electrophoresis, or affinity chromatography, and the like.

[0453] The invention thus also provides methods of producing polypeptides. Briefly, the methods generally involve introducing a nucleic acid construct into a host

cell *in vitro* and culturing the host cell under conditions suitable for expression, then harvesting the polypeptide, either from the culture medium or from the host cell, (e.g., by disrupting the host cell), or both, as described in detail above. The invention also provides methods of producing a polypeptide using cell-free *in vitro* transcription/translation methods, which are well known in the art, also as provided above

[0454] Moreover, the invention provides polypeptides, including polypeptide fragments, as targets for therapeutic intervention, including use in screening assays, for identifying agents that modulate polypeptide level and/or activity, and as targets for antibody and small molecule therapeutics; for example, in the treatment of disorders.

## Methods

[0455] The present invention provides methods of producing a subject polypeptide and provides antibodies that specifically bind to a subject polypeptide. The present invention further provides screening methods for identifying agents that modulate a level or an activity of a subject polypeptide or polynucleotide. The present invention thus also provides agents that modulate a level or an activity of a subject polypeptide or polynucleotide, as well as compositions, including pharmaceutical compositions, comprising a subject agent.

[0456] The present invention further provides methods for treating disorders such as, for example, cancer and other proliferative disorders or conditions, inflammatory and immune disorders, metabolic disorders or conditions and bacterial or viral disorders or conditions.

## Diagnostic and Therapeutic Applications

### Screening and Diagnostic Methods

#### 1. Identifying Biological Molecules that Interact with a Polypeptide

[0457] Formation of a binding complex between a subject polypeptide and an interacting polypeptide or other macromolecule (e.g., DNA, RNA, lipids, polysaccharides, and the like) can be detected using any known method. Suitable methods include: a yeast two-hybrid system (Zhu et al., 1997; Fields and Song, 1989; U.S. Pat. No. 5,283,173; Chien et al. 1991); a mammalian cell two-hybrid method; a fluorescence resonance energy transfer (FRET) assay; a bioluminescence resonance energy transfer (BRET) assay; a fluorescence quenching assay; a fluorescence

anisotropy assay (Jameson and Sawyer, 1995); an immunological assay; and an assay involving binding of a detectably labeled protein to an immobilized protein.

[0458] Immunological assays, and assays involving binding of a detectably labeled protein to an immobilized protein can be performed in a variety of ways. For example, immunoprecipitation assays can be designed such that the complex of protein and an interacting polypeptide is detected by precipitation with an antibody specific for either the protein or the interacting polypeptide.

[0459] FRET detects formation of a binding complex between a subject polypeptide and an interacting polypeptide. It involves the transfer of energy from a donor fluorophore in an excited state to a nearby acceptor fluorophore. For this transfer to take place, the donor and acceptor molecules must be in close proximity (e.g., less than 10 nanometers apart, usually between 10 and 100 Å apart), and the emission spectra of the donor fluorophore must overlap the excitation spectra of the acceptor fluorophore. In these embodiments, a fluorescently labeled subject protein serves as a donor and/or acceptor in combination with a second fluorescent protein or dye.

[0460] Fluorescent proteins can be produced by generating a construct comprising a protein and a fluorescent fusion partner. These are well-known in the art, as described above, including green fluorescent protein (GFP), i.e., a "humanized" version of a GFP, e.g., wherein codons of the naturally-occurring nucleotide sequence are changed to more closely match human codon bias; a GFP derived from *Aequoria victoria* or a derivative thereof, e.g., a "humanized" derivative such as Enhanced GFP, which are available commercially, e.g., from Clontech, Inc.; other fluorescent mutants of a GFP from *Aequoria victoria*, e.g., as described in U.S. Patent No. 6,066,476; 6,020,192; 5,985,577; 5,976,796; 5,968,750; 5,968,738; 5,958,713; 5,919,445; 5,874,304; a GFP from another species such as *Renilla reniformis*, *Renilla mulleri*, or *Ptilosarcus guernei*, as previously described (WO 99/49019; Peelle et al., 2001), "humanized" recombinant GFP (hrGFP) (Stratagene®); any of a variety of fluorescent and colored proteins from Anthozoan species, (e.g., Matz et al., 1999); as well as proteins labeled with other fluorescent dyes, fluorescein and its derivatives, e.g., fluorescein isothiocyanate (FITC), 6-carboxyfluorescein (6-FAM), 6-carboxy-2',4',7',4,7-hexachlorofluorescein (HEX), 5-carboxyfluorescein (5-FAM), 2',7'-dimethoxy-4',5'-dichloro-6-carboxyfluorescein (JOE); rhodamine dyes, e.g., Texas red, phycoerythrin, tetramethylrhodamine, rhodamine, 6-carboxy-X-rhodamine

(ROX); coumarin and its derivatives, e.g., 7-amino-4-methylcoumarin, aminocoumarin; bodipy dyes, such as Bodipy FL; cascade blue; Oregon green; eosins and erythrosins; cyanine dyes, e.g., allophycocyanin, Cy3, Cy5, and N,N,N',N'-tetramethyl-6-carboxyrhodamine (TAMRA); macrocyclic chelates of lanthanide ions, e.g., quantum dye, etc; and chemiluminescent molecules, e.g., luciferases.

[0461] Fluorescent subject proteins can also be generated by producing the subject protein in an auxotrophic strain of bacteria which requires addition of one or more amino acids in the medium for growth. A subject protein-encoding construct that provides for expression in bacterial cells is introduced into the auxotrophic strain, and the bacteria are cultured in the presence of a fluorescent amino acid, which is incorporated into the subject protein produced by the bacterium. The subject protein is then purified from the bacterial culture using standard methods for protein purification.

[0462] BRET is a protein-protein interaction assay based on energy transfer from a bioluminescent donor to a fluorescent acceptor protein. The BRET signal is measured by the ratio of the amount of light emitted by the acceptor to the amount of light emitted by the donor. The ratio of these two values increases as the two proteins are brought into proximity. The BRET assay has been described in the literature (U.S. Patent Nos. 6,020,192; 5,968,750; 5,874,304; Xu, et al. 1999). BRET assays can be performed by analyzing transfer between a bioluminescent donor protein and a fluorescent acceptor protein. Interaction between the donor and acceptor proteins can be monitored by a change in the ratio of light emitted by the bioluminescent and fluorescent proteins. In this application, the subject protein serves as donor and/or acceptor protein.

[0463] Fluorescence anisotropy is a measurement of the rotational mobility of a multi-molecular complex. It can be used to generate information about the binding of one molecule to another, including the affinity and specificity of binding sites. It can be applied to polypeptides or nucleic acids of the present invention.

[0464] Fluorescence quenching measurements are useful in detecting protein multimerization, such as where the subject protein interacts with at least a second protein and, for example, where multimerization interaction is affected by a test agent. As used herein, the term "multimerization" refers to formation of dimers, trimers, tetramers, and higher multimers of the subject protein. Whether a subject protein forms a complex with one or more additional protein molecules can be determined

using any known assay, including assays as described above for interacting proteins. Formation of multimers can also be detected using non-denaturing gel electrophoresis, where multimerized subject protein migrates more slowly than monomeric subject protein. Formation of multimers can also be detected using fluorescence quenching techniques.

[0465] Formation of multimers can also be detected by analytical ultracentrifugation, for example through glycerol or sucrose gradients, and subsequent visualization of a subject protein in gradient fractions by Western blotting or staining of SDS-polyacrylamide gels. Multimers are expected to sediment at defined positions in such gradients. Formation of multimers can also be detected using analytical gel filtration, e.g., in HPLC or FPLC systems, e.g., on columns such as Superdex 200 (Pharmacia Amersham Inc.). Multimers run at defined positions on these columns, and fractions can be analyzed as above. The columns are highly reproducible, allowing one to relate the number and position of peaks directly to the multimerization status of the protein.

## 2. *Detecting mRNA Levels and Monitoring Gene Expression*

[0466] The present invention provides methods for detecting the presence of mRNA in a biological sample. The methods can be used, for example, to assess whether a test compound affects gene expression, either directly or indirectly. The present invention provides diagnostic methods to compare the abundance of a nucleic acid with that of a control value, either qualitatively or quantitatively, and to relate the value to a normal or abnormal expression pattern.

[0467] Methods of measuring mRNA levels are known in the art (Pietu, 1996; Zhao, 1995; Soares, 1997; Raval, 1994; Chalifour, 1994; Stolz, 1996; Hong, 1982; McGraw, 1984; WO 97/27317). These methods generally comprise contacting a sample with a polynucleotide of the invention under conditions that allow hybridization and detecting hybridization, if any, as an indication of the presence of the polynucleotide of interest. Appropriate controls include the use of a sample lacking the polynucleotide mRNA of interest, or the use of a labeled polynucleotide of the same "sense" as a polynucleotide mRNA of interest. Detection can be accomplished by any known method, including, but not limited to, *in situ* hybridization, PCR, RT-PCR, and "Northern" or RNA blotting, or combinations of such techniques, using a suitably labeled subject polynucleotide. A variety of labels and labeling methods for polynucleotides are known in the art and can be used in the



assay methods of the invention. A common method employed is use of microarrays which can be purchased or customized, for example, through conventional vendors such as Affymetrix.

[0468] In some embodiments, the methods involve generating a cDNA copy of an mRNA molecule in a biological sample, and amplifying the cDNA using an isolated primer pairs as described above, i.e., a set of two nucleic acid molecules that serve as forward and reverse primers in an amplification reaction (e.g., a polymerase chain reaction). The primer pairs are chosen to specifically amplify a cDNA copy of an mRNA encoding a polypeptide. A detectable label can be included in the amplification reaction, as provided above. Methods using PCR amplification can be performed on the DNA from a single cell, although it is convenient to use at least about  $10^5$  cells.

[0469] The present invention provides methods for monitoring gene expression. Changes in a promoter or enhancer sequence that can affect gene expression can be examined in light of expression levels of the normal allele by various methods known in the art. Methods for determining promoter or enhancer strength include quantifying the expressed natural protein, and inserting the variant control element into a vector with a quantitative reporter gene such as  $\beta$ -galactosidase, luciferase, or chloramphenicol acetyltransferase (CAT).

### 3. *Detecting Polymorphisms and Mutations*

[0470] Biochemical studies can determine whether a sequence polymorphism in a coding region or control region is associated with disease. Disease-associated polymorphisms can include deletion or truncation of the gene, mutations that alter expression level, or mutations that affect protein function, etc. A number of methods are available to analyze nucleic acids for the presence of a specific sequence, e.g., a disease associated polymorphism. Genomic DNA can be used when large amounts of DNA are available. Alternatively, the region of interest is cloned into a suitable vector and grown in sufficient quantity for analysis. Cells that express the gene provide a source of mRNA, which can be assayed directly or reverse transcribed into cDNA for analysis. The nucleic acid can be amplified by conventional techniques, i.e., PCR, to provide sufficient amounts for analysis. (Saiki et al., 1988; Sambrook et al., 1989, pp.14.2-14.33). Alternatively, various methods are known in the art that utilize oligonucleotide ligation as a means of detecting polymorphisms (Riley et al., 1990; Delahunty et al., 1996).

[0471] The sample nucleic acid, e.g., an amplified or cloned fragment, is analyzed by one of a number of methods known in the art. The nucleic acid can be sequenced by dideoxy nucleotide sequencing, or other methods, and the sequence of bases compared to a wild-type sequence. Hybridization with the variant sequence can also be used to determine its presence, e.g., by Southern blots, dot blots, etc. The hybridization pattern of a control and variant sequence to an array of oligonucleotide probes immobilized on a solid support, as described in US Pat. No. 5,445,934, or WO 95/35505, can also be used as a means of detecting the presence of variant sequences. Single strand conformational polymorphism (SSCP) analysis, denaturing gradient gel electrophoresis (DGGE), and heteroduplex analysis in gel matrices can detect variation as alterations in electrophoretic mobility resulting from conformational changes created by DNA sequence alterations. Alternatively, where a polymorphism creates or destroys a recognition site for a restriction endonuclease, the sample can be digested with that endonuclease, and the products fractionated according to their size to determine whether the fragment was digested. Fractionation can be performed by gel or capillary electrophoresis, for example with acrylamide or agarose gels.

[0472] Screening for mutations in a gene can be based on the functional or antigenic characteristics of the protein. Protein truncation assays are useful in detecting deletions that might affect the biological activity of the protein. Various immunoassays designed to detect polymorphisms in proteins can be used in screening. Where many diverse genetic mutations lead to a particular disease phenotype, functional protein assays have proven to be effective screening tools. The activity of the encoded protein can be determined by comparison with the wild-type protein.

#### 4. Detecting and Monitoring Polypeptide Presence and Biological Activity

[0473] The present invention provides methods for detecting the presence and/or biological activity of a subject polypeptide in a biological sample. The assay used will be appropriate to the biological activity of the particular polypeptide. Thus, e.g., where the biological activity is an enzymatic activity, the method will involve contacting the sample with an appropriate substrate, and detecting the product of the enzymatic reaction on the substrate. Where the biological activity is binding to a second macromolecule, the assay detects protein-protein binding, protein-DNA binding, protein-carbohydrate binding, or protein-lipid binding, as appropriate, using well known assays. Where the biological activity is signal transduction (e.g.,

transmission of a signal from outside the cell to inside the cell) or transport, an appropriate assay is used, such as measurement of intracellular calcium ion concentration, measurement of membrane conductance changes, or measurement of intracellular potassium ion concentration.

[0474] The present invention also provides methods for detecting the presence or measuring the level of a normal or abnormal polypeptide in a biological sample using a specific antibody. The methods generally comprise contacting the sample with a specific antibody and detecting binding between the antibody and molecules of the sample. Specific antibody binding, when compared to a suitable control, is an indication that a polypeptide of interest is present in the sample. Suitable controls include a sample known not to contain the polypeptide, and a sample contacted with a non-specific antibody, e.g., an anti-idiotypic antibody.

[0475] A variety of methods to detect specific antibody-antigen interactions are known in the art, e.g., standard immunohistological methods, immunoprecipitation, enzyme immunoassay, and radioimmunoassay. The specific antibody can be detectably labeled, either directly or indirectly, as described at length herein, and cells are permeabilized to stain cytoplasmic molecules. Briefly, antibodies are added to a cell sample, and incubated for a period of time sufficient to allow binding to the epitope, usually at least about 10 minutes. The antibody may be labeled with radioisotopes, enzymes, fluorescers, chemiluminescers, or other labels for direct detection. Alternatively, specific-binding pairs may be used, involving, e.g., a second stage antibody or reagent that is detectably-labeled, as described above. Such reagents and their methods of use are well known in the art

[0476] Alternatively, a biological sample can be brought into contact with an immobilized antibody on a solid support or carrier, such as nitrocellulose, that is capable of immobilizing cells, cell particles, or soluble proteins. The antibody can be attached (coupled) to an insoluble support, such as a polystyrene plate or a bead. After contacting the sample, the support can then be washed with suitable buffers, followed by contacting with a detectably-labeled specific antibody. Detection methods are known in the art and will be chosen as appropriate to the signal emitted by the detectable label. Detection is generally accomplished in comparison to suitable controls, and to appropriate standards.

[0477] The present invention further provides methods for detecting the presence and/or levels of enzymatic activity of a subject polypeptide in a biological

sample. The methods generally involve contacting the sample with a substrate that yields a detectable product upon being acted upon by a subject polypeptide, and detecting a product of the enzymatic reaction. Further, polypeptides that are subsets of the complete sequences of the subject proteins may be used to identify and investigate parts of the protein important for function.

[0478] The present invention further includes methods for monitoring activity of a polypeptide through observation of phenotypic changes in a cell containing such polypeptide, such as growth or differentiation, or the ability of such a cell to secrete a molecule that can be detected, such as through chemical methods or through its effect on another cell, such as cell activation.

#### *5. Modulating mRNA and Peptides in Biological Samples*

[0479] The present invention provides screening methods for identifying agents that modulate the level of a mRNA molecule of the invention, agents that modulate the level of a polypeptide of the invention, and agents that modulate the biological activity of a polypeptide of the invention. In some embodiments, the assay is cell-free; in others, it is cell-based. Where the screening assay is a binding assay, one or more of the molecules can be joined to a label, where the label can directly or indirectly provide a detectable signal.

[0480] As discussed above, the invention encompasses endogenous polynucleotides of the invention that encode mRNA and/or polypeptides of interest. Again as discussed previously, the invention also encompasses exogenous polynucleotides that encode mRNA or polypeptides of the invention. For example, the polynucleotide can reside within a recombinant vector which is introduced into the cell. For example, a recombinant vector can comprise an isolated transcriptional regulatory sequence which is associated in nature with a nucleic acid, such as a promoter sequence operably linked to sequences coding for a polypeptide of the invention; or the transcriptional control sequences can be operably linked to coding sequences for a polypeptide fusion protein comprising a polypeptide of the invention fused to a polypeptide that facilitates detection.

[0481] In these embodiments, the candidate agent is combined with a cell possessing a polynucleotide transcriptional regulatory element operably linked to a polypeptide-coding sequence of interest, e.g., a subject cDNA or its genomic component; and determining the agent's effect on polynucleotide expression, as measured, for example by the level of mRNA, polypeptide, or fusion polypeptide

[0482] In other embodiments, for example, a recombinant vector can comprise an isolated polynucleotide transcriptional regulatory sequence, such as a promoter sequence, operably linked to a reporter gene (e.g.,  $\beta$ -galactosidase, CAT, luciferase, or other gene that can be easily assayed for expression). In these embodiments, the method for identifying an agent that modulates a level of expression of a polynucleotide in a cell comprises combining a candidate agent with a cell comprising a transcriptional regulatory element operably linked to a reporter gene; and determining the effect of said agent on reporter gene expression.

[0483] Known methods of measuring mRNA levels can be used to identify agents that modulate mRNA levels, including, but not limited to, PCR with detectably-labeled primers. Similarly, agents that modulate polypeptide levels can be identified using standard methods for determining polypeptide levels, including, but not limited to an immunoassay such as ELISA with detectably-labeled antibodies.

[0484] A wide variety of cell-based assays can also be used to identify agents that modulate eukaryotic or prokaryotic mRNA and/or polypeptide levels. Examples include transformed cells that over-express a cDNA construct and cells transformed with a polynucleotide of interest associated with an endogenously-associated promoter operably linked to a reporter gene. A control sample would comprise, for example, the same cell lacking the candidate agent. Expression levels are measured and compared in the test and control samples.

[0485] The cells used in the assay are usually mammalian cells, including, but not limited to, rodent cells and human cells. The cells can be primary cell cultures or can be immortalized cell lines. Cell-based assays generally comprise the steps of contacting the cell with a test agent, forming a test sample, and, after a suitable time, assessing the agent's effect on macromolecule expression. That is, the mammalian cell line is transformed or transfected with a construct that results in expression of the polynucleotide, the cell is contacted with a test agent, and then mRNA or polypeptide levels are detected and measured using conventional assays

[0486] A suitable period of time for contacting the agent with the cell can be determined empirically, and is generally a time sufficient to allow entry of the agent into the cell and to allow the agent to have a measurable effect on subject mRNA and/or polypeptide levels. Generally, a suitable time is between about 10 minutes and about 24 hours, including about 1 to about 8 hours. Alternatively, incubation periods may be between about 0.1 and about 1 hour, selected for example for optimum

activity or to facilitate rapid high-throughput screening. Where the polypeptide is expressed on the cell surface, however, a shorter length of time may be sufficient. Incubations are performed at any suitable temperature, i.e., between about 4°C and about 40°C. The contact and incubation steps can be followed by a washing step to remove unbound components, i.e., a label that would give rise to a background signal during subsequent detection of specifically-bound complexes.

[0487] A variety of assay configurations and protocols are known in the art. For example, one of the components can be bound to a solid support, and the remaining components contacted with the support bound component. Remaining components may be added at different times or at substantially the same time. Further, where the interacting protein is a second subject protein, the effect of the test agent on binding can be determined by determining the effect on multimization of the subject protein.

[0488] The present invention further provides methods of identifying agents that modulate a biological activity of a polypeptide of the invention. The method generally comprises contacting a test agent with a sample containing a subject polypeptide and assaying a biological activity of the subject polypeptide in the presence of the test agent. An increase or a decrease in the assayed biological activity in comparison to the activity in a suitable control (e.g., a sample comprising a subject polypeptide in the absence of the test agent) is an indication that the substance modulates a biological activity of the subject polypeptide. The mixture of components is added in any order that provides for the requisite interaction..

[0489] External and internal processes that can affect modulation of a macromolecule of the invention include, but are not limited to, infection of a cell by a microorganism, including, but not limited to, a bacterium (e.g., *Mycobacterium* spp., *Shigella*, or *Chlamydia*), a protozoan (e.g., *Trypanosoma* spp., *Plasmodium* spp., or *Toxoplasma* spp.), a fungus, a yeast (e.g., *Candida* spp.), or a virus (including viruses that infect mammalian cells, such as human immunodeficiency virus, foot and mouth disease virus, Epstein-Barr virus, and viruses that infect plant cells); change in pH of the medium in which a cell is maintained or a change in internal pH; excessive heat relative to the normal range for the cell or the multicellular organism; excessive cold relative to the normal range for the cell or the multicellular organism; an effector molecule such as a hormone, a cytokine, a chemokine, a neurotransmitter; an ingested or applied drug; a ligand for a cell-surface receptor; a ligand for a receptor that exists

internally in a cell, e.g., a nuclear receptor; hypoxia; light; dark; sleep patterns; electrical charge; ion concentration of the medium in which a cell is maintained or an internal ion concentration, exemplary ions including sodium ions, potassium ions, chloride ions, calcium ions, and the like; presence or absence of a nutrient; metal ions; a transcription factor; mitogens, including, but not limited to, lipopolysaccharide (LPS), pokeweed mitogen; antigens; a tumor suppressor; and cell-cell contact and must be taken into consideration in the screening assay.

[0490] A variety of other reagents can be included in the screening assay. These include salts, neutral proteins, e.g., albumin, detergents, and other compounds that facilitate optimal binding and/or reduce non-specific or background interactions. Reagents that improve the efficiency of the assay, such as protease inhibitors, nuclease inhibitors, or anti-microbial agents, etc., can be used.

[0491] Accordingly, the present invention provides a method for identifying an agent, particularly a biologically active agent that modulates the level of expression of a nucleic acid in a cell, the method comprising: combining a candidate agent to be tested with a cell comprising a nucleic acid that encodes a polypeptide, and determining the agent's effect on polypeptide expression.

[0492] Some embodiments will detect agents that decrease the biological activity of a molecule of the invention. Maximal inhibition of the activity is not always necessary, or even desired, in every instance to achieve a therapeutic effect. Agents that decrease a biological activity can find use in treating disorders associated with the biological activity of the molecule. Alternatively, some embodiments will detect agents that increase a biological activity. Agents that increase a biological activity of a molecule of the invention can find use in treating disorders associated with a deficiency in the biological activity. Agents that increase or decrease a biological activity of a molecule of the invention can be selected for further study, and assessed for physiological attributes, i.e., cellular availability, cytotoxicity, or biocompatibility, and optimized as required. For example, a candidate agent is assessed for any cytotoxic activity it may exhibit toward the cell used in the assay using well-known assays, such as trypan blue dye exclusion, an MTT ([3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl-2 H-tetrazolium bromide]) assay, and the like.

[0493] A variety of different candidate agents can be screened by the above methods. Candidate agents encompass numerous chemical classes, as described above.

[0494] Candidate agents are obtained from a wide variety of sources including libraries of synthetic or natural compounds. Numerous means are available for random and directed synthesis of a wide variety of organic compounds and biomolecules, including expression of randomized oligonucleotides and oligopeptides. For example, random peptide libraries obtained by yeast two-hybrid screens (Xu et al., 1997), phage libraries (Hoogenboom et al., 1998), or chemically generated libraries. Alternatively, libraries of natural compounds in the form of bacterial, fungal, plant and animal extracts are available or readily produced, including antibodies produced upon immunization of an animal with subject polypeptides, or fragments thereof, or with the encoding polynucleotides. Additionally, natural or synthetically produced libraries and compounds are readily modified through conventional chemical, physical and biochemical means, and can be used to produce combinatorial libraries. Further, known pharmacological agents can be subjected to directed or random chemical modifications, such as acylation, alkylation, esterification, and amidification, etc, to produce structural analogs.

#### 6. Kits

[0495] The present invention provides methods for diagnosing disease states based on the detected presence and/or level of polynucleotide or polypeptide in a biological sample, and/or the detected presence and/or level of biological activity of the polynucleotide or polypeptide. These detection methods can be provided as part of a kit. Thus, the invention further provides kits for detecting the presence and/or a level of a polynucleotide or polypeptide in a biological sample and/or or the detected presence and/or level of biological activity of the polynucleotide or polypeptide. Procedures using these kits can be performed by clinical laboratories, experimental laboratories, medical practitioners, or private individuals.

[0496] The kits of the invention will comprise a molecule of the invention. The kits for detecting a polynucleotide will also comprise a moiety that specifically hybridizes to a polynucleotide of the invention. The polynucleotide molecule can be of any length. For example, it can comprise a polynucleotide of at least 6, at least 7, at least 8, or at least 9 contiguous nucleotides of a molecule of the invention. Kits of the invention for detecting a subject polypeptide will comprise a moiety that specifically binds to a polypeptide of the invention; the moiety includes, but is not limited to, a polypeptide-specific antibody.



[0497] The kits are useful in diagnostic applications. For example, the kit is useful to determine whether a given DNA sample isolated from an individual comprises an expressed nucleic acid, a polymorphism, or other variant.

[0498] Kits for detecting polynucleotides comprise a pair of nucleic acids in a suitable storage medium, e.g., a buffered solution, in a suitable container. The pair of isolated nucleic acid molecules serve as primers in an amplification reaction (e.g., a polymerase chain reaction). The kit can further include additional buffers, reagents for polymerase chain reaction (e.g., deoxynucleotide triphosphates (dNTP), a thermostable DNA polymerase, a solution containing  $Mg^{2+}$  ions (e.g.,  $MgCl_2$ ), and other components well known to those skilled in the art for carrying out a polymerase chain reaction). The kit can further include instructions for use, which may be provided in a variety of forms, e.g., printed information, or compact disc, and the like. The kit may further include reagents necessary to extract DNA from a biological sample and reagents for generating a cDNA copy of an mRNA. The kit may optionally provide additional useful components, including, but not limited to, buffers, developing reagents, labels, reacting surfaces, means for detections, control samples, standards, and interpretive information.

[0499] In some embodiments, a kit of the invention for detecting a polynucleotide, such as an mRNA encoding a polypeptide, comprises a pair of nucleic acids that function as "forward" and "reverse" primers that specifically amplify a cDNA copy of the mRNA. The "forward" and "reverse" primers are provided as a pair of isolated nucleic acid molecules, each from about 10 to about 200 nucleotides in length, the first nucleic acid molecule of the pair comprising a sequence of at least about 10 contiguous nucleotides having 100% sequence identity to a nucleic acid sequence shown in from SEQ ID NOS.: 1 - 104, and the second nucleic acid molecule of the pair comprising a sequence of at least about 10 contiguous nucleotides having 100% sequence identity to the reverse complement of a nucleic acid sequence shown in SEQ ID NOS.: 1 - 104, wherein the sequence of the second nucleic acid molecule is located 3' of the nucleic acid sequence of the first nucleic acid molecule. The primer nucleic acids are prepared using any known method, e.g., automated synthesis. In some embodiments, one or both members of the pair of nucleic acid molecules comprise a detectable label.

[0500] Where the kit provides for polypeptide detection, it can include one or more specific antibodies. In some embodiments, the antibody specific to the

polypeptide is detectably labeled. In other embodiments, the antibody specific to the polypeptide is not labeled; instead, a second, detectably-labeled antibody is provided that binds to the specific antibody. The kit may further include blocking reagents, buffers, and reagents for developing and/or detecting the detectable marker. The kit may further include instructions for use, controls, and interpretive information.

[0501] Where the kit provides for detecting enzymatic activity, it includes a substrate that provides for a detectable product when acted upon by a polypeptide of interest. The kit may further include reagents necessary to detect and develop the detectable marker.

[0502] The present invention provides for kits with unit doses of an active agent. These agents are described in more detail below. In some embodiments, the agent is provided in oral or injectable doses. Such kits will comprise containers containing the unit doses and an informational package insert describing the use and attendant benefits of the drugs in treating a condition of interest.

#### *Therapeutic Compositions*

[0503] The invention further provides agents identified using a screening assay of the invention, and compositions comprising the agents, subject polypeptides, subject polynucleotides, recombinant vectors, and/or host cells, including pharmaceutical compositions for therapeutic administration. The subject compositions can be formulated using well-known reagents and methods. These compositions can include a buffer, which is selected according to the desired use of the agent, polypeptide, polynucleotide, recombinant vector, or host cell, and can also include other substances appropriate to the intended use. Those skilled in the art can readily select an appropriate buffer, a wide variety of which are known in the art, suitable for an intended use.

#### *1. Excipients and Formulations*

[0504] In some embodiments, compositions are provided in formulation with pharmaceutically acceptable excipients, a wide variety of which are known in the art (Gennaro, 2000; Ansel et al., 1999; Kibbe et al., 2000). Pharmaceutically acceptable excipients, such as vehicles, adjuvants, carriers or diluents, are readily available to the public. Moreover, pharmaceutically acceptable auxiliary substances, such as pH adjusting and buffering agents, tonicity adjusting agents, stabilizers, wetting agents and the like, are readily available to the public.

[0505] In pharmaceutical dosage forms, the compositions of the invention can be administered in the form of their pharmaceutically acceptable salts, or they can also be used alone or in appropriate association, as well as in combination, with other pharmaceutically active compounds. The subject compositions are formulated in accordance to the mode of potential administration. Administration of the agents can be achieved in various ways, including oral, buccal, nasal, rectal, parenteral, intraperitoneal, intradermal, transdermal, subcutaneous, intravenous, intra-arterial, intracardiac, intraventricular, intracranial, intratracheal, and intrathecal administration, etc., or otherwise by implantation or inhalation. Thus, the subject compositions can be formulated into preparations in solid, semi-solid, liquid or gaseous forms, such as tablets, capsules, powders, granules, ointments, solutions, suppositories, injections, inhalants and aerosols. The following methods and excipients are merely exemplary and are in no way limiting.

[0506] For oral preparations, the agents, polynucleotides, and polypeptides can be used alone or in combination with appropriate additives to make tablets, powders, granules or capsules, for example, with conventional additives, such as lactose, mannitol, corn starch, or potato starch; with binders, such as crystalline cellulose, cellulose derivatives, acacia, corn starch, or gelatins; with disintegrators, such as corn starch, potato starch, or sodium carboxymethylcellulose; with lubricants, such as talc or magnesium stearate; and if desired, with diluents, buffering agents, moistening agents, preservatives, and flavoring agents.

[0507] Suitable excipient vehicles are, for example, water, saline, dextrose, glycerol, ethanol, or the like, and combinations thereof. In addition, if desired, the vehicle can contain minor amounts of auxiliary substances such as wetting or emulsifying agents or pH buffering agents. Actual methods of preparing such dosage forms are known, or will be apparent, to those skilled in the art (Remington, 1985). The composition or formulation to be administered will, in any event, contain a quantity of the agent adequate to achieve the desired state in the subject being treated.

[0508] The agents, polynucleotides, and polypeptides can be formulated into preparations for injection by dissolving, suspending or emulsifying them in an aqueous or nonaqueous solvent, such as vegetable or other similar oils, synthetic aliphatic acid glycerides, esters of higher aliphatic acids or propylene glycol; and if desired, with conventional additives such as solubilizers, isotonic agents, suspending

agents, emulsifying agents, stabilizers and preservatives. Other formulations for oral or parenteral delivery can also be used, as conventional in the art

[0509] The agents, polynucleotides, and polypeptides can be utilized in aerosol formulation to be administered via inhalation. The compounds of the present invention can be formulated into pressurized acceptable propellants such as dichlorodifluoromethane, propane, nitrogen, and the like. Further, the agent, polynucleotides, or polypeptide composition may be converted to powder form for administration intranasally or by inhalation, as conventional in the art.

[0510] Furthermore, the agents can be made into suppositories by mixing with a variety of bases such as emulsifying bases or water-soluble bases. The compounds of the present invention can be administered rectally via a suppository. The suppository can include vehicles such as cocoa butter, carbowaxes and polyethylene glycols, which melt at body temperature, yet are solidified at room temperature.

[0511] A polynucleotide, polypeptide, or other modulator, can also be introduced into tissues or host cells by other routes, such as viral infection, microinjection, or vesicle fusion. For example, expression vectors can be used to introduce nucleic acid compositions into a cell as described above. Further, jet injection can be used for intramuscular administration (Furth et al., 1992). The DNA can be coated onto gold microparticles, and delivered intradermally by a particle bombardment device, or "gene gun" as described in the literature (Tang et al., 1992), where gold microprojectiles are coated with the DNA, then bombarded into skin cells.

[0512] Unit dosage forms for oral or rectal administration such as syrups, elixirs, and suspensions can be provided wherein each dosage unit, for example, teaspoonful, tablespoonful, tablet, or suppository, contains a predetermined amount of the composition containing one or more agents. Similarly, unit dosage forms for injection or intravenous administration can comprise the agent(s) in a composition as a solution in sterile water, normal saline or another pharmaceutically acceptable carrier.

## 2. Active Agents (or Modulators)

[0513] The nucleic acid, polypeptide, and modulator compositions of the subject invention find use as therapeutic agents in situations where one wishes to modulate an activity of a subject polypeptide in a host, particularly the activity of the subject polypeptides, or to provide or inhibit the activity at a particular anatomical

site. Thus, the compositions are useful in treating disorders associated with an activity of a subject polypeptide. The following provides further details of active agents of the present invention.

*a) Antisense Oligonucleotides*

[0514] In certain embodiments of the invention, the active agent is an agent that modulates, and generally decreases or down regulates, the expression of a gene encoding a target protein in a host, i.e., antisense molecules. Anti-sense reagents include antisense oligonucleotides (ODN), i.e., synthetic ODN having chemical modifications from native nucleic acids, or nucleic acid constructs that express such anti-sense molecules as RNA. The antisense sequence is complementary to the mRNA of the targeted gene, and inhibits expression of the targeted gene products. Antisense molecules inhibit gene expression through various mechanisms, e.g., by reducing the amount of mRNA available for translation, through activation of RNase H, or steric hindrance. One or a combination of antisense molecules can be administered, where a combination can comprise multiple different sequences.

[0515] Antisense molecules can be produced by expression of all or a part of the target gene sequence in an appropriate vector, where the transcriptional initiation is oriented such that an antisense strand is produced as an RNA molecule. Alternatively, the antisense molecule is a synthetic oligonucleotide. Antisense oligonucleotides can be chemically synthesized by methods known in the art (Wagner et al., 1993; Milligan et al., 1993). Oligonucleotides can be chemically modified from the native phosphodiester structure to increase their intracellular stability and binding affinity, for example, as described in detail above. Antisense oligonucleotides will generally be at least about 7, at least about 12, or at least about 20 nucleotides in length, and not more than about 500, not more than about 50, or not more than about 35 nucleotides in length, where the length is governed by efficiency of inhibition, and specificity, including absence of cross-reactivity, and the like. Short oligonucleotides, of from about 7 to about 8 bases in length, can be strong and selective inhibitors of gene expression (Wagner et al., 1996).

[0516] A specific region or regions of the endogenous sense strand mRNA sequence is chosen to be complemented by the antisense sequence. Selection of a specific sequence for the oligonucleotide can use an empirical method, where several candidate sequences are assayed for inhibition of expression of the target gene in an *in*

*vitro* or animal model. A combination of sequences can also be used, where several regions of the mRNA sequence are selected for antisense complementation.

[0517] As an alternative to anti-sense inhibitors, catalytic nucleic acid compounds, e.g., ribozymes, or anti-sense conjugates can be used to inhibit gene expression. Ribozymes can be synthesized *in vitro* and administered to the patient, or can be encoded in an expression vector, from which the ribozyme is synthesized in the targeted cell (WO 9523225; Beigelman et al., 1995). Examples of oligonucleotides with catalytic activity are described in WO 9506764. Conjugates of anti-sense ODN with a metal complex, e.g., terpyridyl Cu(II), capable of mediating mRNA hydrolysis are described in Bashkin *et al.*, 1995.

#### *b) Interfering RNA*

[0518] In some embodiments, the active agent is an interfering RNA (RNAi), including dsRNAi. RNA interference provides a method of silencing eukaryotic genes. Double stranded RNA can induce the homology-dependent degradation of its cognate mRNA in *C. elegans*, fungi, plants, *Drosophila*, and mammals (Gaudilliere et al., 2002). Use of RNAi to reduce a level of a particular mRNA and/or protein is based on the interfering properties of double-stranded RNA derived from the coding regions of a gene. The technique reduces the time between identifying an interesting gene sequence and understanding its function, and thus is an efficient high-throughput method for disrupting gene function (O'Neil, 2001). RNAi can also help identify the biochemical mode of action of a drug and to identify other genes encoding products that can respond or interact with specific compounds.

[0519] In one embodiment of the invention, complementary sense and antisense RNAs derived from a substantial portion of the subject polynucleotide are synthesized *in vitro*. The resulting sense and antisense RNAs are annealed in an injection buffer, and the double-stranded RNA injected or otherwise introduced into the subject, i.e., in food or by immersion in buffer containing the RNA (Gaudilliere et al., 2002; O'Neil et al., 2001; WO99/32619). In another embodiment, dsRNA derived from a gene of the present invention is generated *in vivo* by simultaneously expressing both sense and antisense RNA from appropriately positioned promoters operably linked to coding sequences in both sense and antisense orientations.

#### *c) Peptides and Modified Peptides*

[0520] In some embodiments of the present invention, the active agent is a peptide. Suitable peptides include peptides of from about 3 amino acids to about 50,

from about 5 to about 30, or from about 10 to about 25 amino acids in length. In some embodiments, a peptide has a sequence of from about 3 amino acids to about 50, from about 5 to about 30, or from about 10 to about 25 amino acids of corresponding naturally-occurring protein. In some embodiments, a peptide exhibits one or more of the following activities: inhibits binding of a subject polypeptide to an interacting protein or other molecule; inhibits subject polypeptide binding to a second polypeptide molecule; inhibits a signal transduction activity of a subject polypeptide; inhibits an enzymatic activity of a subject polypeptide; or inhibits a DNA binding activity of a subject polypeptide.

[0521] Peptides can include naturally-occurring and non-naturally occurring amino acids. Peptides can comprise D-amino acids, a combination of D- and L-amino acids, and various "designer" amino acids (e.g.,  $\beta$ -methyl amino acids,  $\alpha$ -methyl amino acids, and N $\alpha$ -methyl amino acids, etc.) to convey special properties. Additionally, peptides can be cyclic. Peptides can include non-classical amino acids in order to introduce particular conformational motifs. Any known non-classical amino acid can be used. Non-classical amino acids include, but are not limited to, 1,2,3,4-tetrahydroisoquinoline-3-carboxylate; (2S,3S)-methylphenylalanine, (2S,3R)-methyl-phenylalanine, (2R,3S)-methyl-phenylalanine and (2R,3R)-methyl-phenylalanine; 2-aminotetrahydronaphthalene-2-carboxylic acid; hydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylate;  $\beta$ -carboline (D and L); HIC (histidine isoquinoline carboxylic acid); and HIC (histidine cyclic urea). Amino acid analogs and peptidomimetics can be incorporated into a peptide to induce or favor specific secondary structures, including, but not limited to, LL-Acp (LL-3-amino-2-propenidone-6-carboxylic acid), a  $\beta$ -turn inducing dipeptide analog;  $\beta$ -sheet inducing analogs;  $\beta$ -turn inducing analogs;  $\alpha$ -helix inducing analogs;  $\gamma$ -turn inducing analogs; Gly-Ala turn analogs; amide bond isostere; or tetrazol, and the like.

[0522] A peptide can be a depsipeptide, which can be linear or cyclic (Kuisle et al., 1999). Linear depsipeptides can comprise rings formed through S-S bridges, or through an hydroxy or a mercapto group of an hydroxy-, or mercapto-amino acid and the carboxyl group of another amino- or hydroxy-acid but do not comprise rings formed only through peptide or ester links derived from hydroxy carboxylic acids. Cyclic depsipeptides contain at least one ring formed only through peptide or ester links, derived from hydroxy carboxylic acids.

[0523] Peptides can be cyclic or bicyclic. For example, the C-terminal carboxyl group or a C-terminal ester can be induced to cyclize by internal displacement of the -OH or the ester (-OR) of the carboxyl group or ester respectively with the N-terminal amino group to form a cyclic peptide. For example, after synthesis and cleavage to give the peptide acid, the free acid is converted to an activated ester by an appropriate carboxyl group activator such as dicyclohexylcarbodiimide (DCC) in solution, for example, in methylene chloride ( $\text{CH}_2\text{Cl}_2$ ), dimethyl formamide (DMF) mixtures. The cyclic peptide is then formed by internal displacement of the activated ester with the N-terminal amine. Internal cyclization as opposed to polymerization can be enhanced by use of very dilute solutions. Methods for making cyclic peptides are well known in the art.

[0524] The term "bicyclic" refers to a peptide with two ring closures formed by covalent linkages between amino acids. A covalent linkage between two nonadjacent amino acids constitutes a ring closure, as does a second covalent linkage between a pair of adjacent amino acids which are already linked by a covalent peptide linkage. The covalent linkages forming the ring closures can be amide linkages, i.e., the linkage formed between a free amino on one amino acid and a free carboxyl of a second amino acid, or linkages formed between the side chains or "R" groups of amino acids in the peptides. Thus, bicyclic peptides can be "true" bicyclic peptides, i.e., peptides cyclized by the formation of a peptide bond between the N-terminus and the C-terminus of the peptide, or they can be "depsi-bicyclic" peptides, i.e., peptides in which the terminal amino acids are covalently linked through their side chain moieties.

[0525] A desamino or descarboxy residue can be incorporated at the terminal ends of the peptide, so that there is no terminal amino or carboxyl group, to decrease susceptibility to proteases or to restrict conformation. C-terminal functional groups include amide, amide lower alkyl, amide di (lower alkyl), lower alkoxy, hydroxy, and carboxy, and the lower ester derivatives thereof, and the pharmaceutically acceptable salts thereof.

[0526] In addition to the foregoing N-terminal and C-terminal modifications, a peptide or peptidomimetic can be modified with or covalently coupled to one or more of a variety of hydrophilic polymers to increase solubility and circulation half-life of the peptide. Suitable nonproteinaceous hydrophilic polymers for coupling to a peptide include, but are not limited to, polyalkylethers as exemplified by polyethylene



glycol and polypropylene glycol, polylactic acid, polyglycolic acid, polyoxyalkenes, polyvinylalcohol, polyvinylpyrrolidone, cellulose and cellulose derivatives, dextran, and dextran derivatives. Generally, such hydrophilic polymers have an average molecular weight ranging from about 500 to about 100,000 daltons, from about 2,000 to about 40,000 daltons, or from about 5,000 to about 20,000 daltons. The peptide can be derivatized with or coupled to such polymers using any of the methods set forth in Zallipsky, 1995; Monfardini et al., 1995; U.S. Pat. Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192; 4,179,337, or WO 95/34326.

*d) Antibodies*

[0527] The invention provides antibodies that specifically recognize a particular polypeptide. Antibodies are obtained by immunizing a host animal with peptides, polynucleotides encoding polypeptides, or cells, each comprising all or a portion of the target protein ("immunogen"). Suitable host animals include rodents (e.g., mouse, rat, guinea pig, hamster), cattle (e.g., sheep, pig, cow, horse, goat), cat, dog, chicken, primate, monkey, and rabbit. The origin of the protein immunogen can be any species, including mouse, human, rat, monkey, avian, insect, reptile, or crustacean. The host animal will generally be a different species than the immunogen, e.g., a human protein used to immunize mice. Methods of antibody production are well known in the art (Howard and Bethell, 2000; Harlow et al., 1998; Harlow and Lane, 1988).

[0528] The immunogen can comprise the complete protein, or fragments and derivatives thereof, or proteins expressed on cell surfaces. Immunogens comprise all or a part of one of the subject proteins, where these amino acids contain post-translational modifications, such as glycosylation, found on the native target protein. Immunogens comprising protein extracellular domains are produced in a variety of ways known in the art, e.g., expression of cloned genes using conventional recombinant methods, or isolation from tumor cell culture supernatants, etc. The immunogen can also be expressed *in vivo* from a polynucleotide encoding the immunogenic peptide introduced into the host animal.

[0529] Polyclonal antibodies are prepared by conventional techniques. These include immunizing the host animal *in vivo* with the target protein (or immunogen) in substantially pure form, for example, comprising less than about 1% contaminant. The immunogen can comprise the complete target protein, fragments, or derivatives thereof. To increase the immune response of the host animal, the target

protein can be combined with an adjuvant; suitable adjuvants include alum, dextran, sulfate, large polymeric anions, and oil & water emulsions, e.g., Freund's adjuvant (complete or incomplete). The target protein can also be conjugated to synthetic carrier proteins or synthetic antigens. The target protein is administered to the host, usually intradermally, with an initial dosage followed by one or more, usually at least two, additional booster dosages. Following immunization, blood from the host will be collected, followed by separation of the serum from blood cells. The immunoglobulin present in the resultant antiserum can be further fractionated using known methods, such as ammonium salt fractionation, or DEAE chromatography and the like.

[0530] The method of producing polyclonal antibodies can be varied in some embodiments of the present invention. For example, instead of using a single substantially isolated polypeptide as an immunogen, one may inject a number of different immunogens into one animal for simultaneous production of a variety of antibodies. In addition to protein immunogens, the immunogens can be nucleic acids (e.g., in the form of plasmids or vectors) that encode the proteins, with facilitating agents, such as liposomes, microspheres, etc, or without such agents, such as "naked" DNA.

[0531] Antibodies can also be prepared using a library approach. Briefly, mRNA is extracted from the spleens of immunized animals to isolate antibody-encoding sequences. The extracted mRNA may be used to make cDNA libraries. Such a cDNA library may be normalized and subtracted in a manner conventional in the art, for example, to subtract out cDNA hybridizing to mRNA of non-immunized animals. The remaining cDNA may be used to create proteins and for selection of antibody molecules or fragments that specifically bind to the immunogen. The cDNA clones of interest, or fragments thereof, can be introduced into an *in vitro* expression system to produce the desired antibodies, as described herein.

[0532] In a further embodiment, polyclonal antibodies can be prepared using phage display libraries, conventional in the art. In this method, a collection of bacteriophages displaying antibody properties on their surfaces are made to contact subject polypeptides, or fragments thereof. Bacteriophages displaying antibody properties that specifically recognize the subject polypeptides are selected, amplified, for example, in *E. coli*, and harvested. Such a method typically produces single chain antibodies

[0533] Monoclonal antibodies are also produced by conventional techniques, such as fusing an antibody-producing plasma cell with an immortal cell to produce hybridomas. Suitable animals will be used, e.g., to raise antibodies against a mouse polypeptide of the invention, the host animal will generally be a hamster, guinea pig, goat, chicken, or rabbit, and the like. Generally, the spleen and/or lymph nodes of an immunized host animal provide the source of plasma cells, which are immortalized by fusion with myeloma cells to produce hybridoma cells. Culture supernatants from individual hybridomas are screened using standard techniques to identify clones producing antibodies with the desired specificity. The antibody can be purified from the hybridoma cell supernatants or from ascites fluid present in the host by conventional techniques, e.g., affinity chromatography using antigen, e.g., the subject protein, bound to an insoluble support, i.e., protein A sepharose, etc.

[0534] The antibody can be produced as a single chain, instead of the normal multimeric structure of the immunoglobulin molecule. Single chain antibodies have been previously described (i.e., Jost et al., 1994). DNA sequences encoding parts of the immunoglobulin, for example, the variable region of the heavy chain and the variable region of the light chain are ligated to a spacer, such as one encoding at least about four small neutral amino acids, i.e., glycine or serine. The protein encoded by this fusion allows the assembly of a functional variable region that retains the specificity and affinity of the original antibody.

[0535] The invention also provides intrabodies that are intracellularly expressed single-chain antibody molecules designed to specifically bind and inactivate target molecules inside cells. Intrabodies have been used in cell assays and in whole organisms (Chen et al., 1994; Hassanzadeh et al., 1998). Inducible expression vectors can be constructed with intrabodies that react specifically with a protein of the invention. These vectors can be introduced into host cells and model organisms.

[0536] The invention also provides "artificial" antibodies, e.g., antibodies and antibody fragments produced and selected *in vitro*. In some embodiments, these antibodies are displayed on the surface of a bacteriophage or other viral particle, as described above. In other embodiments, artificial antibodies are present as fusion proteins with a viral or bacteriophage structural protein, including, but not limited to, M13 gene III protein. Methods of producing such artificial antibodies are well known in the art (U.S. Patent Nos. 5,516,637; 5,223,409; 5,658,727; 5,667,988; 5,498,538;

5,403,484; 5,571,698; and 5,625,033). The artificial antibodies, selected for example, on the basis of phage binding to selected antigens, can be fused to a Fc fragment of an immunoglobulin for use as a therapeutic, as described, for example, in US 5,116,964 or WO 99/61630. Antibodies of the invention can be used to modulate biological activity of cells, either directly or indirectly. A subject antibody can modulate the activity of a target cell, with which it has primary interaction, or it can modulate the activity of other cells by exerting secondary effects, i.e., when the primary targets interact or communicate with other cells. The antibodies of the invention can be administered to mammals, and the present invention includes such administration, particularly for therapeutic and/or diagnostic purposes in humans.

[0537] Antibodies may be administered by injection systemically, such as by intravenous injection; or by injection or application to the relevant site, such as by direct injection into a tumor, or direct application to the site when the site is exposed in surgery; or by topical application, such as if the disorder is on the skin, for example.

[0538] For *in vivo* use, particularly for injection into humans, in some embodiments it is desirable to decrease the antigenicity of the antibody. An immune response of a recipient against the antibody may potentially decrease the period of time that the therapy is effective. Methods of humanizing antibodies are known in the art. The humanized antibody can be the product of an animal having transgenic human immunoglobulin genes, e.g., constant region genes (e.g., Grosveld and Kolias, 1992; Murphy and Carter, 1993; Pinkert, 1994; and International Patent Applications WO 90/10077 and WO 90/04036). Alternatively, the antibody of interest can be engineered by recombinant DNA techniques to substitute the CH1, CH2, CH3, hinge domains, and/or the framework domain with the corresponding human sequence (see, e.g., WO 92/02190). Both polyclonal and monoclonal antibodies made in non-human animals may be "humanized" before administration to human subjects.

[0539] Chimeric immunoglobulin genes constructed with immunoglobulin cDNA are known in the art (Liu et al. 1987a; Liu et al. 1987b). Messenger RNA is isolated from a hybridoma or other cell producing the antibody and used to produce cDNA. The cDNA of interest can be amplified by the polymerase chain reaction using specific primers (U.S. Patent nos. 4,683,195 and 4,683,202). Alternatively, a library is made and screened to isolate the sequence of interest. The DNA sequence encoding the variable region of the antibody is then fused to human constant region

sequences. The sequences of human constant regions genes are known in the art (Kabat et al., 1991). Human C region genes are readily available from known clones. The choice of isotype will be guided by the desired effector functions, such as complement fixation, or antibody-dependent cellular cytotoxicity. IgG1, IgG3 and IgG4 isotypes, and either of the kappa or lambda human light chain constant regions can be used. The chimeric, humanized antibody is then expressed by conventional methods.

[0540] Consensus sequences of heavy ("H") and light ("L") J regions can be used to design oligonucleotides for use as primers to introduce useful restriction sites into the J region for subsequent linkage of V region segments to human C region segments. C region cDNA can be modified by site directed mutagenesis to place a restriction site at the analogous position in the human sequence.

[0541] A convenient expression vector for producing antibodies is one that encodes a functionally complete human CH or CL immunoglobulin sequence, with appropriate restriction sites engineered so that any VH or VL sequence can be easily inserted and expressed, such as plasmids, retroviruses, YACs, or EBV derived episomes, and the like. In such vectors, splicing usually occurs between the splice donor site in the inserted J region and the splice acceptor site preceding the human C region, and also at the splice regions that occur within the human CH exons. Polyadenylation and transcription termination occur at native chromosomal sites downstream of the coding regions. The resulting chimeric antibody can be joined to any strong promoter, including retroviral LTRs, e.g., SV-40 early promoter, (Okayama, et al. 1983), Rous sarcoma virus LTR (Gorman et al. 1982), and Moloney murine leukemia virus LTR (Grosschedl et al. 1985), or native immunoglobulin promoters.

[0542] In yet other embodiments, the antibodies can be fully human antibodies. For example, xenogenic antibodies, which are produced in animals that are transgenic for human antibody genes, can be employed. By xenogenic human antibodies is meant antibodies that are fully human antibodies, with the exception that they are produced in a non-human host that has been genetically engineered to express human antibodies. (e.g., WO 98/50433; WO 98,24893 and WO 99/53049).

[0543] Antibody fragments, such as Fv, F(ab')<sub>2</sub> and Fab can be prepared by cleavage of the intact protein, e.g., by protease or chemical cleavage. These fragments can include heavy and light chain variable regions. Alternatively, a

truncated gene can be designed, e.g., a chimeric gene encoding a portion of the F(ab')<sub>2</sub> fragment that includes DNA sequences encoding the CH1 domain and hinge region of the H chain, followed by a translational stop codon. The antibodies of the present invention may be administered alone or in combination with other molecules for use as a therapeutic, for example, by linking the antibody to cytotoxic agent, as discussed above, or to a radioactive molecule. Radioactive antibodies that are specific to a cancer cell, disease cell, or virus-infected cell may be able to deliver a sufficient dose of radioactivity to kill such cancer cell, disease cell, or virus-infected cell. The antibodies of the present invention can also be used in assays for detection of the subject polypeptides. In some embodiments, the assay is a binding assay that detects binding of a polypeptide with an antibody specific for the polypeptide; the subject polypeptide or antibody can be immobilized, while the subject polypeptide and/or antibody can be detectably-labeled. For example, the antibody can be directly labeled or detected with a labeled secondary antibody. That is, suitable, detectable labels for antibodies include direct labels, which label the antibody to the protein of interest, and indirect labels, which label an antibody that recognizes the antibody to the protein of interest.

[0544] These labels include radioisotopes, including, but not limited to <sup>64</sup>Cu, <sup>67</sup>Cu, <sup>90</sup>Y, <sup>124</sup>I, <sup>125</sup>I, <sup>131</sup>I, <sup>137</sup>Cs, <sup>186</sup>Re, <sup>211</sup>At, <sup>212</sup>Bi, <sup>213</sup>Bi, <sup>223</sup>Ra, <sup>241</sup>Am, and <sup>244</sup>Cm; enzymes having detectable products (e.g., luciferase,  $\beta$ -galactosidase, and the like); fluorescers and fluorescent labels, e.g., as provided herein; fluorescence emitting metals, e.g., <sup>152</sup>Eu, or others of the lanthanide series, attached to the antibody through metal chelating groups such as EDTA; chemiluminescent compounds, e.g., luminol, isoluminol, or acridinium salts; and bioluminescent compounds, e.g., luciferin, or aequorin (green fluorescent protein), specific binding molecules, e.g., magnetic particles, microspheres, nanospheres, and the like.

[0545] Alternatively, specific-binding pairs may be used, involving, e.g., a second stage antibody or reagent that is detectably-labeled and that can amplify the signal. For example, a primary antibody can be conjugated to biotin, and horseradish peroxidase-conjugated streptavidin added as a second stage reagent. Digoxin and antidigoxin provide another such pair. In other embodiments, the secondary antibody can be conjugated to an enzyme such as peroxidase in combination with a substrate that undergoes a color change in the presence of the peroxidase. The absence or presence of antibody binding can be determined by various methods, including flow

cytometry of dissociated cells, microscopy, radiography, or scintillation counting. Such reagents and their methods of use are well known in the art.

*e) Peptide Aptamers*

[0546] Another suitable agent for modulating an activity of a subject polypeptide is a peptide aptamer. Peptide aptamers are peptides or small polypeptides that act as dominant inhibitors of protein function. Peptide aptamers specifically bind to target proteins, blocking their functional ability (Kolonin and Finley, 1998). Due to the highly selective nature of peptide aptamers, they can be used not only to target a specific protein, but also to target specific functions of a given protein (e.g., a signaling function). Further, peptide aptamers can be expressed in a controlled fashion by use of promoters which regulate expression in a temporal, spatial or inducible manner. Peptide aptamers act dominantly, therefore, they can be used to analyze proteins for which loss-of-function mutants are not available.

[0547] Peptide aptamers that bind with high affinity and specificity to a target protein can be isolated by a variety of techniques known in the art. Peptide aptamers can be isolated from random peptide libraries by yeast two-hybrid screens (Xu et al., 1997). They can also be isolated from phage libraries (Hoogenboom et al., 1998) or chemically generated peptides/libraries.

*Therapeutic Applications: Methods of Use*

[0548] The instant invention provides various therapeutic methods. In some embodiments, methods of modulating, including increasing and inhibiting, a biological activity of a subject protein are provided. In some embodiments, methods of modulating an enzymatic activity of a subject protein are provided. In some embodiments, methods of increasing the level of enzymatically active subject protein are provided, while in some embodiments, methods of decreasing a level of enzymatically active subject protein are provided.

[0549] In some embodiments, methods of modulating enzymatic activity of a subject protein are provided. In other embodiments, methods of modulating a signal transduction activity of a subject protein are provided. In further embodiments, methods of modulating interaction of a subject protein with another, interacting protein or other macromolecule (e.g., DNA, carbohydrate, lipid) are provided. In further embodiments, methods of modulating transport activity of a subject protein are provided. In further embodiments, methods of modulating phospholipase activity of a subject protein are provided. In further embodiments, methods of modulating

polymerase activity of a subject protein are provided. In further embodiments, methods of modulating nuclease activity of a subject protein are provided.

[0550] As mentioned above, an effective amount of the active agent (e.g., small molecule, antibody specific for a subject polypeptide, a subject polypeptide, or a subject polynucleotide) is administered to the host, where "effective amount" means a dosage sufficient to produce a desired effect or result. In some embodiments, the desired result is at least a reduction in a given biological activity of a subject polypeptide as compared to a control, for example, a decreased level of enzymatically active subject protein in the individual, or in a localized anatomical site in the individual. In further embodiments, the desired result is at least an increase in a biological activity of a subject polypeptide as compared to a control, for example an increased level of enzymatically active subject protein in the individual, or in a localized anatomical site in the individual.

[0551] Typically, the compositions of the instant invention will contain from less than about 1% to about 95% of the active ingredient, about 10% to about 50%. Generally, between about 100 mg and about 500 mg will be administered to a child and between about 500 mg and about 5 grams will be administered to an adult.

[0552] Other effective dosages can be readily determined by one of ordinary skill in the art through routine trials establishing dose response curves, for example, the amount of agent necessary to increase a level of active subject polypeptide can be calculated from *in vitro* experimentation. Those of skill will readily appreciate that dose levels can vary as a function of the specific compound, the severity of the symptoms, and the susceptibility of the subject to side effects, and preferred dosages for a given compound are readily determinable by those of skill in the art by a variety of means. For example, in order to calculate the polypeptide, polynucleotide, or modulator dose, those skilled in the art can use readily available information with respect to the amount necessary to have the desired effect, depending upon the particular agent used.

[0553] The active agent(s) can be administered to the host via any convenient means capable of resulting in the desired result. Administration is generally by injection and often by injection to a localized area. The frequency of administration will be determined by the care given based on patient responsiveness. For example, the agents may be administered daily, weekly, or as conventionally determined appropriate.



[0554] A variety of hosts are treatable according to the subject methods. The host, or patient, may be from any animal species, and will generally be mammalian, e.g., primate sp., e.g., monkeys, chimpanzees, and particularly humans; rodents, including mice, rats and hamsters, guinea pig; rabbits; cattle, including equines, bovines, pig, sheep, goat, canines; felines; etc. Animal models are of interest for experimental investigations, providing a model for treatment of human disease.

#### *Proliferative Conditions*

[0555] In some embodiments, a protein of the present invention is involved in the control of cell proliferation, and an agent of the invention inhibits undesirable cell proliferation. Such agents are useful for treating disorders that involve abnormal cell proliferation, including, but not limited to, cancer, psoriasis, and scleroderma. Whether a particular agent and/or therapeutic regimen of the invention is effective in reducing unwanted cellular proliferation, e.g., in the context of treating cancer, can be determined using standard methods. For example, the number of cancer cells in a biological sample (e.g., blood, a biopsy sample, and the like), can be determined. The tumor mass can be determined using standard radiological or biochemical methods.

[0556] Tumors that can be treated using the methods of the instant invention include carcinomas, e.g., colorectal, prostate, breast, bone, kidney, skin, melanoma, ductal, endometrial, stomach or other organ of the gastrointestinal tract, pancreatic, mesothelioma, dysplastic oral mucosa, invasive oral cancer, non-small cell lung carcinoma ("NSCL"), transitional and squamous cell urinary carcinoma; brain cancer and neurological malignancies, e.g., neuroblastoma, glioblastoma, astrocytoma, and gliomas; lymphomas and leukemias such as myeloid leukemia, myelogenous leukemia, hematological malignancies, such as childhood acute leukemia, non-Hodgkin's lymphomas, chronic lymphocytic leukemia, malignant cutaneous T-cell lymphoma, mycosis fungoides, non-MF cutaneous T-cell lymphoma, lymphomatoid papulosis, T-cell rich cutaneous lymphoid hyperplasia, bullous pemphigoid, discoid lupus erythematosus, lichen planus, and human follicular lymphoma; cancers of the reproductive system, e.g., cervical and ovarian cancers and testicular cancers; liver cancers including hepatocellular carcinoma ("HCC") and tumors of the biliary duct; multiple myelomas; tumors of the esophageal tract; other lung cancers and tumors including small cell and clear cell; Hodgkin's lymphomas; adenocarcinoma; and sarcomas, including soft tissue sarcomas.

*Immunotherapeutic Approaches to Proliferative Conditions*

[0557] The polynucleotides, polypeptides, and modulators of the present invention find use in immunotherapy of hyperproliferative disorders, including cancer, neoplastic, and paraneoplastic disorders. That is, the subject molecules can correspond to tumor antigens, of which 1770 have been identified to date (Yu and Restifo, 2002). Immunotherapeutic approaches include passive immunotherapy and vaccine therapy and can accomplish both generic and antigen-specific cancer immunotherapy.

[0558] Passive immunity approaches involve antibodies of the invention that are directed toward specific tumor-associated antigens. Such antibodies can eradicate systemic tumors at multiple sites, without eradicating normal cells. In some embodiments, the antibodies are combined with radioactive components, as provided above, for example, combining the antibody's ability to specifically target tumors with the added lethality of the radioisotope to the tumor DNA.

[0559] Useful antibodies comprise a discrete epitope or a combination of nested epitopes, i.e., a 10-mer epitope and associated peptide multimers incorporating all potential 8-mers and 9-mers, or overlapping epitopes (Dutoit et al., 2002). Thus a single antibody can interact with one or more epitopes. Further, the antibody can be used alone or in combination with different antibodies, that all recognize either a single or multiple epitopes.

[0560] Neutralizing antibodies can provide therapy for cancer and proliferative disorders. Neutralizing antibodies that specifically recognize a secreted protein or peptide of the invention can bind to the secreted protein or peptide, e.g., in a bodily fluid or the extracellular space, thereby modulating the biological activity of the secreted protein or peptide. For example, neutralizing antibodies specific for secreted proteins or peptides that play a role in stimulating the growth of cancer cells can be useful in modulating the growth of cancer cells. Similarly, neutralizing antibodies specific for secreted proteins or peptides that play a role in the differentiation of cancer cells can be useful in modulating the differentiation of cancer cells.

[0561] Vaccine therapy involves the use of polynucleotides, polypeptides, or agents of the invention as immunogens for tumor antigens (Machiels et al., 2002). For example, peptide-based vaccines of the invention include unmodified subject polypeptides, fragments thereof, and MHC class I and class II-restricted peptide

(Knutson et al., 2001), comprising, for example, the disclosed sequences with universal, nonspecific MHC class II-restricted epitopes. Peptide-based vaccines comprising a tumor antigen can be given directly, either alone or in conjunction with other molecules. The vaccines can also be delivered orally by producing the antigens in transgenic plants that can be subsequently ingested (U.S. Patent No. 6,395,964).

[0562] In some embodiments, antibodies themselves can be used as antigens in anti-idiotypic vaccines. That is, administering an antibody to a tumor antigen stimulates B cells to make antibodies to that antibody, which in turn recognize the tumor cells

[0563] Nucleic acid-based vaccines can deliver tumor antigens as polynucleotide constructs encoding the antigen. Vaccines comprising genetic material, such as DNA or RNA, can be given directly, either alone or in conjunction with other molecules. Administration of a vaccine expressing a molecule of the invention, e.g., as plasmid DNA, leads to persistent expression and release of the therapeutic immunogen over a period of time, helping to control unwanted tumor growth.

[0564] In some embodiments, nucleic acid-based vaccines encode subject antibodies. In such embodiments, the vaccines (e.g., DNA vaccines) can include post-transcriptional regulatory elements, such as the post-transcriptional regulatory acting RNA element (WPRE) derived from Woodchuck Hepatitis Virus. These post-transcriptional regulatory elements can be used to target the antibody, or a fusion protein comprising the antibody and a co-stimulatory molecule, to the tumor microenvironment (Pertl et al., 2003).

[0565] Besides stimulating anti-tumor immune responses by inducing humoral responses, vaccines of the invention can also induce cellular responses, including stimulating T-cells that recognize and kill tumor cells directly. For example, nucleotide-based vaccines of the invention encoding tumor antigens can be used to activate the CD8<sup>+</sup> cytotoxic T lymphocyte arm of the immune system.

[0566] In some embodiments, the vaccines activate T-cells directly, and in others they enlist antigen-presenting cells to activate T-cells. Killer T-cells are primed, in part, by interacting with antigen-presenting cells, i.e., dendritic cells. In some embodiments, plasmids comprising the nucleic acid molecules of the invention enter antigen-presenting cells, which in turn display the encoded tumor-antigens that

contribute to killer T-cell activation. Again, the tumor antigens can be delivered as plasmid DNA constructs, either alone or with other molecules.

[0567] In further embodiments, RNA can be used. For example, dendritic cells can be transfected with RNA encoding tumor antigens (Heiser et al., 2002; Mitchell and Nair, 2000). This approach overcomes the limitations of obtaining sufficient quantities of tumor material, extending therapy to patients otherwise excluded from clinical trials. For example, a subject RNA molecule isolated from tumors can be amplified using RT-PCR. In some embodiments, the RNA molecule of the invention is directly isolated from tumors and transfected into dendritic cells with no intervening cloning steps.

[0568] In some embodiments the molecules of the invention are altered such that the peptide antigens are more highly antigenic than in their native state. These embodiments address the need in the art to overcome the poor *in vivo* immunogenicity of most tumor antigens by enhancing tumor antigen immunogenicity via modification of epitope sequences (Yu and Restifo, 2002).

[0569] Another recognized problem of cancer vaccines is the presence of preexisting neutralizing antibodies. Some embodiments of the present invention overcome this problem by using viral vectors from non-mammalian natural hosts, i.e., avian pox viruses. Alternative embodiments that also circumvent preexisting neutralizing antibodies include genetically engineered influenza viruses, and the use of "naked" plasmid DNA vaccines that contain DNA with no associated protein. (Yu and Restifo, 2002).

[0570] All of the immunogenic methods of the invention can be used alone or in combination with other conventional or unconventional therapies. For example, immunogenic molecules can be combined with other molecules that have a variety of antiproliferative effects, or with additional substances that help stimulate the immune response, i.e., adjuvants or cytokines.

[0571] For example, in some embodiments, nucleic acid vaccines encode an alphaviral replicase enzyme, in addition to tumor antigens. This recently discovered approach to vaccine therapy successfully combines therapeutic antigen production with the induction of the apoptotic death of the tumor cell (Yu and Restifo, 2002).

[0572] In certain other embodiments, a DNA or RNA vaccine of the present invention can also be directed against the production of blood vessels in the vicinity of the tumor, a process called antiangiogenesis, thereby depriving the cancer cells of

nutrients. For example, the antiangiogenic molecules angiostatin (a fragment of plasminogen), endostatin (a fragment of collagen XVIII), interferon- $\gamma$ , interferon- $\gamma$  inducible protein 10, interleukin 12, thrombospondin, platelet factor-4, calreticulin, or its protein fragment vasostatin can be used to treat tumors by suppressing neovascularization and thereby inhibiting growth (Cheng et al., 2001). The antiangiogenesis approach can be used alone, or in conjunction with molecules directed to tumor antigens.

[0573] Furthermore, adjuvants can be used in conjunction with the antibodies and vaccines disclosed herein. Adjuvants help boost the general immune response, for example, concentrating immune cells to the specific area where they are needed. They can be added to a cancer vaccine itself or administered separately, and in some embodiments, a viral vector can be engineered to display adjuvant proteins on its surface.

[0574] Cytokines can also be used to help stimulate immune response. Cytokines act as chemical messengers, recruiting immune cells that help the killer T-cells to the site of attack. An example of a cytokine is granulocyte-macrophage colony-stimulating factor (GM-CSF), which stimulates the proliferation of antigen-presenting cells, thus boosting an organism's response to a cancer vaccine. As with adjuvants, cytokines can be used in conjunction with the antibodies and vaccines disclosed herein. For example, they can be incorporated into the antigen-encoding plasmid or introduced via a separate plasmid, and in some embodiments, a viral vector can be engineered to display cytokines on its surface.

#### *Inflammation and Immunity*

[0575] In other embodiments, e.g., where the subject polypeptide is involved in modulating inflammation or immune function, the invention provides agents for treating such inflammation or immune disorders. Disease states that are treatable using formulations of the invention include various types of arthritis such as rheumatoid arthritis and osteoarthritis, autoimmune thyroiditis, various chronic inflammatory conditions of the skin, such as psoriasis, the intestine, such as inflammatory bowel disease (IBD), insulin-dependent diabetes, autoimmune diseases such as multiple sclerosis (MS), intestinal immune disorders and systemic lupus erythematosus (SLE), allergic diseases, transplant rejections, adult respiratory distress syndrome, atherosclerosis, ischemic diseases due to closure of the peripheral

vasculature, cardiac vasculature, and vasculature in the central nervous system (CNS). After reading the present disclosure, those skilled in the art will recognize other disease states and/or symptoms which might be treated and/or mitigated by the administration of formulations of the present invention.

[0576] Neutralizing antibodies can provide immunosuppressive therapy for inflammatory and autoimmune disorders. Neutralizing antibodies can be used to treat disorders such as, for example, multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, transplant rejection, and psoriasis. Neutralizing antibodies that specifically recognize a secreted protein or peptide of the invention can bind to the secreted protein or peptide, e.g., in a bodily fluid or the extracellular space, thereby modulating the biological activity of the secreted protein or peptide. For example, neutralizing antibodies specific for secreted proteins or peptides that play a role in activating immune cells are useful as immunosuppressants.

#### *Disorders Related to Cell Death*

[0577] Where a polypeptide of the invention is involved in modulating cell death, an agent of the invention is useful for treating conditions or disorders relating to cell death (e.g., DNA damage, cell death, apoptosis). Cell death-related indications that can be treated using the methods of the invention to reduce cell death in a eukaryotic cell, include, but are not limited to, cell death associated with Alzheimer's disease, Parkinson's disease, rheumatoid arthritis, autoimmune thyroiditis, septic shock, sepsis, stroke, central nervous system inflammation, intestinal inflammation, osteoporosis, ischemia, reperfusion injury, cardiac muscle cell death associated with cardiovascular disease, polycystic kidney disease, cell death of endothelial cells in cardiovascular disease, degenerative liver disease, multiple sclerosis, amyotrophic lateral sclerosis, cerebellar degeneration, ischemic injury, cerebral infarction, myocardial infarction, acquired immunodeficiency syndrome (AIDS), myelodysplastic syndromes, aplastic anemia, male pattern baldness, and head injury damage. Also included are conditions in which DNA damage to a cell is induced by external conditions, including but not limited to irradiation, radiomimetic drugs, hypoxic injury, chemical injury, and damage by free radicals. Also included are any hypoxic or anoxic conditions, e.g., conditions relating to or resulting from ischemia, myocardial infarction, cerebral infarction, stroke, bypass heart surgery, organ transplantation, and neuronal damage, etc.

[0578] DNA damage can be detected using any known method, including, but not limited to, a Comet assay (commercially available from Trevigen, Inc.), which is based on alkaline lysis of labile DNA at sites of damage; and immunological assays using antibodies specific for aberrant DNA structures, e.g., 8-OHdG.

[0579] Cell death can be measured using any known method, and is generally measured using any of a variety of known methods for measuring cell viability. Such assays are generally based on entry into the cell of a detectable compound (or a compound that becomes detectable upon interacting with, or being acted on by, an intracellular component) that would normally be excluded from a normal, living cell by its structurally and functionally intact cell membrane. Such compounds include substrates for intracellular enzymes, including, but not limited to, a fluorescent substrate for esterase; dyes that are excluded from living cells, including, but not limited to, trypan blue; and DNA-binding compounds, including, but not limited to, an ethidium compound such as ethidium bromide and ethidium homodimer, and propidium iodide.

[0580] Apoptosis, or programmed cell death, is a regulated process leading to cell death via a series of well-defined morphological changes. Programmed cell death provides a balance for cell growth and multiplication, eliminating unnecessary cells. The default state of the cell is to remain alive. A cell enters the apoptotic pathway when an essential factor is removed from the extracellular environment or when an internal signal is activated. Genes and proteins of the invention that suppress the growth of tumors by activating cell death provide the basis for treatment strategies for hyperproliferative disorders and conditions.

[0581] Apoptosis can be assayed using any known method. Assays can be conducted on cell populations or an individual cell, and include morphological assays and biochemical assays. A non-limiting example of a method of determining the level of apoptosis in a cell population is TUNEL (TdT-mediated dUTP nick-end labeling) labeling of the 3'-OH free end of DNA fragments produced during apoptosis (Gavrieli et al., 1992). The TUNEL method consists of catalytically adding a nucleotide, which has been conjugated to a chromogen system, a fluorescent tag, or the 3'-OH end of the 180-bp (base pair) oligomer DNA fragments, in order to detect the fragments. The presence of a DNA ladder of 180-bp oligomers is indicative of apoptosis. Procedures to detect cell death based on the TUNEL method are available

commercially, e.g., from Boehringer Mannheim (Cell Death Kit) and Oncor (Apoptag Plus).

[0582] Another marker that is currently available is annexin, sold under the trademark APOPTEST™. This marker is used in the "Apoptosis Detection Kit," which is also commercially available, e.g., from R&D Systems. During apoptosis, a cell membrane's phospholipid asymmetry changes such that the phospholipids are exposed on the outer membrane. Annexins are a homologous group of proteins that bind phospholipids in the presence of calcium. A second reagent, propidium iodide (PI), is a DNA binding fluorochrome. When a cell population is exposed to both reagents, apoptotic cells stain positive for annexin and negative for PI, necrotic cells stain positive for both, live cells stain negative for both. Other methods of testing for apoptosis are known in the art and can be used, including, e.g., the method disclosed in U.S. Patent No. 6,048,703.

#### *Other Pathological Conditions*

[0583] Other pathological conditions that can be treated using the methods of the instant invention include disorders of hematopoiesis, cell differentiation, disorders of ion channels, e.g., cystic fibrosis, and tissue or organ hypertrophy, bacterial disorders, viral disorders, including acquired immunodeficiency syndrome (AIDS), angiogenesis, metastasis, metabolic disorders such as diabetes and obesity, cardiovascular disorders such as congestive heart failure and stroke, male erectile dysfunction, and the disorders described throughout the specification.

#### **Investigative Applications**

[0584] The subject nucleic acid compositions find use in a variety of different investigative applications. Applications of interest include identifying genomic DNA sequence using molecules of the invention, identifying homologs of molecules of the invention, creating a source of novel promoter elements, identifying expression regulatory factors, creating a source of probes and primers for hybridization applications, identifying expression patterns in biological specimens; preparing cell or animal models to investigate the function of the molecules of the invention, and preparing *in vitro* models to investigate the function of the molecules of the invention.

#### **Genomic DNA Sequences**

[0585] Human genomic polynucleotide sequences corresponding to molecules of the present invention are identified by conventional means, such as, for



example, by probing a genomic DNA library with all or a portion of the polynucleotide sequences.

### *Homologs*

[0586] Homologs are identified by any of a number of methods. By using probes, particularly labeled probes of DNA sequences, one can isolate homologous or related genes, as described in detail above. Briefly, a fragment of the provided cDNA can be used as a hybridization probe against a cDNA library from the target organism of interest, under various stringency conditions, e.g., low stringency conditions. The probe can be a large fragment, or one or more short degenerate primers, and is typically labeled. Sequence identity can be determined by hybridization under stringent conditions, as described in detail above. Nucleic acids having a region of substantial identity or sequence similarity to the provided nucleic acid sequences, for example allelic variants, related genes, or genetically altered versions of the gene, bind to the provided sequences under less stringent hybridization conditions.

### **Promoter Elements and Expression Regulatory Factors**

[0587] The sequence of the 5' flanking region can be utilized as promoter elements, including enhancer binding sites that provide for tissue-specific expression and developmental regulation in tissues where the subject genes are expressed, providing promoters that mimic the native pattern of expression. Naturally occurring polymorphisms in the promoter region are useful for determining natural variations in expression, particularly those that may be associated with disease. Promoters or enhancers that regulate the transcription of the polynucleotides of the present invention are obtainable by use of PCR techniques using human tissues, and one or more of the present primers.

[0588] Alternatively, mutations can be introduced into the promoter region to determine the effect of altering expression in experimentally defined systems. Methods for the identification of specific DNA motifs involved in the binding of transcriptional factors are known in the art, for example sequence similarity to known binding motifs, and gel retardation studies (Blackwell et al., 1995; Mortlock et al., 1996; Joulin and Richard-Foy, 1995).

[0589] The regulatory sequences can be used to identify *cis* acting sequences required for transcriptional or translational regulation of expression, especially in different tissues or stages of development, and to identify *cis* acting sequences and *trans*-acting factors that regulate or mediate expression. Such transcription or

translational control regions can be operably linked to a gene in order to promote expression of wild type genes or of proteins of interest in cultured cells, embryonic, fetal or adult tissues, and for gene therapy (Hooper, 1993).

#### Primers and Probes

[0590] Small DNA fragments are useful as primers for reactions that involve nucleic acid hybridization, as described in detail above. Briefly, pairs of primers will be used in amplification reactions, such as PCR. Amplification primers hybridize to complementary strands of DNA, for example, under stringent conditions, and will prime towards each other. In some embodiments a pair of primers will generate an amplification product of at least about 50 nt, or at least about 100 nt. Algorithms for the selection of primer sequences are generally known, and are available in commercial software packages.

[0591] The nucleotides can also be used as probes to identify genomic DNA or gene expression in a biological specimen, as described above and as is well established in the art. Briefly, DNA or mRNA is isolated from a cell sample. Detection of mRNA hybridizing to the subject sequence is indicative of gene expression in the sample. The mRNA can be amplified by RT-PCR, using reverse transcriptase to form a complementary DNA strand, followed by polymerase chain reaction amplification using primers specific for the subject DNA sequences. Alternatively, the mRNA sample is separated by gel electrophoresis, transferred to a suitable support, *e.g.*, nitrocellulose, nylon, *etc.*, and then probed with a fragment of the subject nucleotides as a probe. Other techniques, such as oligonucleotide ligation assays, *in situ* hybridizations, and hybridization to probes arrayed on a solid chip may also find use.

#### Targeted Mutations for *In Vivo* and *In Vitro* Models

[0592] The sequence of a gene according to the subject invention, including flanking promoter regions and coding regions, can be mutated in various ways known in the art to generate targeted changes, *i.e.*, changes in promoter strength, or sequence of the encoded protein, *etc.* The DNA sequence or protein product of such a mutation will usually be substantially similar to the sequences provided herein. The sequence changes can be substitutions, insertions, deletions, or a combination thereof. Deletions can further include larger changes, such as deletions of a domain or exon.

[0593] Techniques for *in vitro* mutagenesis of cloned genes are known. Examples of protocols for site specific mutagenesis may be found in Gustin et al.,

1993; Barany 1985; Colicelli et al., 1985; Prentki et al., 1984. Methods for site specific mutagenesis can be found in Sambrook et al., 1989 (pp. 15.3-15.108); Weiner et al., 1993; Sayers et al. 1992; Jones and Winistorfer; Barton et al., 1990; Marotti and Tomich 1989; and Zhu, 1989. Such mutated genes can be used to study structure-function relationships of the subject proteins, or to alter properties of the protein that affect its function or regulation. Other modifications of interest include epitope tagging, e.g., with hemagglutinin (HA), FLAG, or *c-myc*. For studies of subcellular localization, fluorescent fusion proteins can be used.

[0594] The subject nucleic acids can be used to generate transgenic, non-human animals and/or site-specific gene modifications in cell lines; suitable methods are known in the art (Grosveld and Kollias, 1992; Hooper, 1993; Murphy and Carter, 1993; Pinkert, 1994). Thus, in some embodiments, the invention provides a non-human transgenic animal comprising, as a transgene integrated into the genome of the animal, a nucleic acid molecule comprising a sequence encoding a subject polypeptide in operable linkage with a promoter, such that the subject polypeptide-encoding nucleic acid molecule is expressed in a cell of the animal. Either a complete or partial sequence of a gene native to the host can be introduced. Alternatively, a complete or partial sequence of a gene exogenous to the host animal, e.g., a human sequence of the subject invention, can be introduced. Transgenic animals can be made through homologous recombination, where the endogenous locus is altered. Thus, DNA constructs for homologous recombination will comprise at least a portion of the human gene or of a gene native to the species of the host animal, wherein the gene has the desired genetic modification(s), and includes regions of homology to the target locus. Methods for generating mammalian cells having targeted gene modifications through homologous recombination are known in the art (Keown et al., 1990).

[0595] Alternatively, a nucleic acid construct is randomly integrated into the genome. Vectors for stable integration include plasmids, retroviruses and other animal viruses, and YACs. DNA constructs for random integration need not include regions of homology to mediate recombination.

[0596] Conveniently, markers for positive and negative selection are included. A detectable marker, such as *lac Z* can be introduced into a locus at which up-regulation of expression will result in a detectable change in phenotype.

[0597] Transformed ES or embryonic cells can be used to produce transgenic animals. An embryonic stem (ES) cell line can be a source of embryonic stem cells, or they can be newly obtained from a host animal, e.g., a mouse, rat, or guinea pig. The cells are grown on an appropriate fibroblast-feeder layer or in the presence of leukemia inhibiting factor (LIF). Following transformation, the cells are plated for growth onto a feeder layer in an appropriate medium. Cells containing the relevant construct can be detected by employing a selective medium and analyzing them for the occurrence of homologous recombination or integration of the construct. Positive colonies can be used for embryo manipulation and blastocyst injection. Blastocysts are obtained from 4 to 6 week old super-ovulated females. The ES cells are trypsinized, and the modified cells are injected into the blastocoel of the blastocyst. After injection, the blastocysts are returned to each uterine horn of pseudopregnant female animals that proceed to term. The resulting offspring are screened for the construct. By providing for a different phenotype of the blastocyst and the genetically modified cells, chimeric progeny can be readily detected.

[0598] The chimeric animals are screened for the presence of the modified gene and males and females having the modification are mated to produce homozygous progeny. If the gene alterations cause lethality at some point in development, tissues or organs can be maintained as allogeneic or congenic grafts or transplants, or in *in vitro* culture. The transgenic animals can be any non-human mammal.

[0599] The modified cells or animals are useful in the study of gene function and regulation. For example, a series of small deletions and/or substitutions can be made in the host's native gene to determine the role of different exons in biological processes such as oncogenesis or signal transduction. Of interest is the use of genes to construct transgenic animal models for cancer, where expression of the subject protein is specifically reduced or absent. Specific constructs of interest include anti-sense constructs, which will block expression, expression of dominant negative mutations, and gene over-expression.

[0600] One can also provide for expression of the gene, e.g., a subject gene, or variants thereof, in cells or tissues where it is not normally expressed, at levels not normally present in such cells or tissues, or at abnormal times of development. One can also generate host cells (including host cells in transgenic animals) that comprise a heterologous nucleic acid molecule which encodes a polypeptide which functions to

modulate expression of an endogenous promoter or other transcriptional regulatory region, or the biological activity of a subject polypeptide.

[0601] The transgenic animals can also be used in functional studies, for example drug screening, to determine the effect of a candidate drug on a biological activity of a subject polypeptide.

**Table 1. Characteristics of the Fantom Mouse Protein With the Highest Degree of Similarity to the Claimed Sequences**

FP ID	Fantom Top Hit Annotation
HG1000214N0_160000_gene_prediction1	pre-B lymphocyte gene 1 [Mus musculus]
HG1000323N0_160000_gene_prediction1	lipoprotein lipase [Mus musculus]
HG1000323N0_160000_gene_prediction2	similar to procollagen, type V, alpha 2 [Mus musculus]
HG1000327N0_1000_gene_prediction1	unnamed protein product [Mus musculus]
HG1000327N0_160000_gene_prediction1	unnamed protein product [Mus musculus]
HG1000434N0_160000_gene_prediction1	uromodulin; Tamm-Horsfall glycoprotein [Mus musculus]
HG1000449N0_160000_gene_prediction1	trefoil factor 1 [Mus musculus]
HG1000807N0_160000_gene_prediction1	IGFBP-like protein [Mus musculus]
HG1000807N0_5000_gene_prediction1	gi 9055246 ref NP_061211.1  IGFBP-like protein [Mus musculus]
HG1001280N0_160000_gene_prediction1	gi 26336763 dbj BAC32064.1  unnamed protein product [Mus musculus]
HG1000193N0_160000_gene_prediction1	gi 21595011 gb AAH31409.1  RIKEN cDNA 2410030O07 gene [Mus musculus]
HG1000286N0_160000_gene_prediction1	gi 303678 dbj BAA02298.1  47-kDa heat shock protein [Mus musculus]
HG1000569N0_160000_gene_prediction1	gi 20881983 ref XP_122793.1  similar to heat-stable antigen-related hypothetical protein HSA-C - mouse [Mus musculus]
HG1000992N0_160000_gene_prediction1	gi 26331916 dbj BAC29688.1  unnamed protein product [Mus musculus]
HG1001148N0_160000_gene_prediction1	gi 6752962 ref NP_033744.1  a disintegrin and metalloprotease domain 15 (metargidin); a disintegrin and metalloproteinase domain (ADAM) 15 (metargidin) [Mus musculus]
HG1001185N0_160000_gene_prediction2	gi 26329785 dbj BAC2863.1  unnamed protein product [Mus musculus]
HG1001280N0_5000_gene_prediction1	gi 26336763 dbj BAC32064.1  unnamed protein product [Mus musculus]
HG1001302N0_160000_gene_prediction2	gi 20136122 gb AAM11539.1  matrilin-2 [Mus musculus]
HG1000361N0_160000_gene_prediction1	gi 20867549 ref XP_125932.1  RIKEN cDNA 9030421L11 [Mus musculus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000361N0_20000_gene_prediction1	gi 26330472 dbj BAC28966.1  unnamed protein product [Mus musculus]
HG1000792N0_160000_gene_prediction1	gi 27229118 ref NP_082129.2  RIKEN cDNA 061006F02 [Mus musculus]
HG1000934N0_160000_gene_prediction1	gi 20867549 ref XP_125932.1  RIKEN cDNA 9030421L11 [Mus musculus]
HG1000976N0_160000_gene_prediction1	gi 11967965 ref NP_071879.1  cytochrome P450, subfamily IVF, polypeptide 14 (leukotriene B4 omega hydroxylase) [Mus musculus]
HG1000992N0_10000_gene_prediction1	gi 26331916 dbj BAC29688.1  unnamed protein product [Mus musculus]
HG1001185N0_1000_gene_prediction1	gi 26329785 dbj BAC28631.1  unnamed protein product [Mus musculus]
HG1001185N0_160000_gene_prediction1	gi 26329785 dbj BAC28631.1  unnamed protein product [Mus musculus]
HG1001185N0_1000_gene_prediction2	gi 26329785 dbj BAC28631.1  unnamed protein product [Mus musculus]
HG1001185N0_5000_gene_prediction1	gi 26329785 dbj BAC28631.1  unnamed protein product [Mus musculus]
HG1001280N0_10000_gene_prediction1	gi 26336763 dbj BAC32064.1  unnamed protein product [Mus musculus]
HG1000361N0_10000_gene_prediction1	gi 26330472 dbj BAC28966.1  unnamed protein product [Mus musculus]
HG1001381N0_1000_gene_prediction1	gi 26343077 dbj BAC35195.1  unnamed protein product [Mus musculus]
HG1000263N0_5000_gene_prediction1	gi 26360198 dbj BAB25612.2  unnamed protein product [Mus musculus]
HG1001052N0_0_gene_prediction1	gi 20072693 gb AAH27297.1  Similar to cyclin K [Mus musculus]
HG1000498N0_160000_gene_prediction1	gi 26352844 dbj BAC40052.1  unnamed protein product [Mus musculus]
HG1000579N0_160000_gene_prediction1	gi 26330550 dbj BAC29005.1  unnamed protein product [Mus musculus]
HG1000685N0_160000_gene_prediction1	gi 6753236 ref NP_033915.1  calcium channel, voltage dependent, alpha2/delta subunit 3; alpha 2 delta-3 [Mus musculus]
HG1000191N0_160000_gene_prediction1	gi 13385832 ref NP_080608.1  RIKEN cDNA 1810055D05 [Mus musculus]
HG1000296N0_160000_gene_prediction2	gi 25054735 ref XP_192839.1  ATPase, class II, type 9B [Mus musculus]
HG1000346N0_1000_gene_prediction1	gi 26330504 dbj BAC28982.1  unnamed protein product [Mus musculus]
HG1000963N0_5000_gene_prediction1	gi 12963665 ref NP_075892.1  mesoderm

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
	development candiate 2; RIKEN cDNA 2210015O11 gene [Mus musculus]
HG1000610N0_160000_gene_prediction1	gi 26335037 dbj BAC31219.1  unnamed protein product [Mus musculus]
HG1000342N0_160000_gene_prediction1	gi 20881983 ref XP_122793.1  similar to heat-stable antigen-related hypothetical protein HSA-C - mouse [Mus musculus]
HG1000342N0_160000_gene_prediction2	gi 20881983 ref XP_122793.1  similar to heat-stable antigen-related hypothetical protein HSA-C - mouse [Mus musculus]
HG1000650N0_20000_gene_prediction1	gi 20270210 ref NP_083847.1  RIKEN cDNA 1110001A12 [Mus musculus]
HG1000191N0_160000_gene_prediction2	gi 13385832 ref NP_080608.1  RIKEN cDNA 1810055D05 [Mus musculus]
HG1000449N0_160000_gene_prediction3	gi 6755773 ref NP_035705.1  trefoil factor 3, intestinal [Mus musculus]
HG1000181N0_20000_gene_prediction1	gi 26334755 dbj BAC31078.1  unnamed protein product [Mus musculus]
HG1001058N0_160000_gene_prediction1	gi 20344262 ref XP_110959.1  similar to LD31582p [Drosophila melanogaster] [Mus musculus]
HG1000187N0_160000_gene_prediction2	gi 26346705 dbj BAC37001.1  unnamed protein product [Mus musculus]
HG1000191N0_1000_gene_prediction1	gi 13385832 ref NP_080608.1  RIKEN cDNA 1810055D05 [Mus musculus]
HG1000319N0_160000_gene_prediction1	gi 25021456 ref XP_207950.1  similar to pORF2 [Mus musculus domesticus]
HG1000137N0_0_gene_prediction1	gi 20843789 ref XP_133814.1  similar to hypothetical protein IMAGE3455200 [Homo sapiens] [Mus musculus]
HG1000191N0_5000_gene_prediction1	gi 12842346 dbj BAB25565.1  unnamed protein product [Mus musculus]
HG1000622N0_160000_gene_prediction1	gi 25022040 ref XP_204233.1  similar to ORF2 [Mus musculus domesticus]
HG1000390N0_1000_gene_prediction1	gi 20892585 ref XP_147977.1  RIKEN cDNA 2610001E17 [Mus musculus]
HG1001350N0_5000_gene_prediction1	gi 13386102 ref NP_080892.1  RIKEN cDNA 1500026D16 [Mus musculus]
HG1000327N0_160000_gene_prediction2	gi 26324414 dbj BAC25961.1  unnamed protein product [Mus musculus]
HG1000179N0_160000_gene_prediction1	gi 20862121 ref XP_146270.1  similar to putative alpha 1,3-fucosyl transferase [Mus musculus]
HG1000806N0_20000_gene_prediction	gi 23592855 ref XP_129487.2  hypothetical



WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
1	protein MGC40674 [Mus musculus]
HG1000991N0_160000_gene_prediction1	gi 6755338 ref NP_036013.1  ring finger protein 13 [Mus musculus]
HG1001489N0_20000_gene_prediction1	gi 23592855 ref XP_129487.2  hypothetical protein MGC40674 [Mus musculus]
HG1001038N0_5000_gene_prediction1	gi 20892051 ref XP_148657.1  similar to Lethal(2)neighbour of tid protein 2 (NOT53) [Mus musculus]
HG1001376N0_160000_gene_prediction2	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1001376N0_20000_gene_prediction2	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1001478N0_10000_gene_prediction1	gi 6979907 gb AAF34647.1 AF221103_1 kinesin-related protein KIFC5B [Mus musculus]
HG1000806N0_160000_gene_prediction1	gi 23592855 ref XP_129487.2  hypothetical protein MGC40674 [Mus musculus]
HG1000409N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000884N0_160000_gene_prediction1	gi 26329055 dbj BAC28266.1  unnamed protein product [Mus musculus]
HG1000575N0_160000_gene_prediction1	gi 20889984 ref XP_129281.1  RIKEN cDNA 4930538D17 [Mus musculus]
HG1000403N0_160000_gene_prediction1	gi 26340168 dbj BAC33747.1  unnamed protein product [Mus musculus]
HG1000906N0_10000_gene_prediction1	gi 20836822 ref XP_130277.1  similar to Plakophilin 4 (p0071) [Mus musculus]
HG1001201N0_160000_gene_prediction1	gi 26341746 dbj BAC34535.1  unnamed protein product [Mus musculus]
HG1000485N0_160000_gene_prediction1	gi 23597904 ref XP_129263.2  protein phosphatase 1, regulatory (inhibitor) subunit 3C [Mus musculus]
HG1000328N0_160000_gene_prediction1	gi 26336731 dbj BAC32048.1  unnamed protein product [Mus musculus]
HG1000231N0_160000_gene_prediction1	gi 26341312 dbj BAC34318.1  unnamed protein product [Mus musculus]
HG1001257N0_10000_gene_prediction1	gi 26346593 dbj BAC36945.1  unnamed protein product [Mus musculus]
HG1000026N0_5000_gene_prediction1	gi 9506367 ref NP_062425.1  ATP-binding cassette, sub-family B, member 10; ATP-binding cassette, sub-family B (MDR/TAP), member 12; Abc-mitochondrial erythroid [Mus musculus]
HG1000300N0_160000_gene_prediction1	gi 12846244 dbj BAB27089.1  unnamed protein

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
n1	product [Mus musculus]
HG1000109N0_160000_gene_prediction1	gi 22779909 ref NP_690028.1  RIKEN cDNA 2700083B01 [Mus musculus]
HG1000617N0_20000_gene_prediction1	gi 7949115 ref NP_058079.1  Ser/Arg-related nuclear matrix protein; plenty-of-prolines-101; serine/arginine repetitive matrix protein 1 [Mus musculus]
HG1001110N0_160000_gene_prediction1	gi 22779909 ref NP_690028.1  RIKEN cDNA 2700083B01 [Mus musculus]
HG1001334N0_160000_gene_prediction1	gi 26332062 dbj BAC29761.1  unnamed protein product [Mus musculus]
HG1001376N0_160000_gene_prediction3	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1000026N0_20000_gene_prediction1	gi 9506367 ref NP_062425.1  ATP-binding cassette, sub-family B, member 10; ATP-binding cassette, sub-family B (MDR/TAP), member 12; Abc-mitochondrial erythroid [Mus musculus]
HG1000276N0_1000_gene_prediction1	gi 19527228 ref NP_598768.1  DNA segment, Chr 10, ERATO Doi 214, expressed [Mus musculus]
HG1000822N0_160000_gene_prediction2	gi 6680195 ref NP_032255.1  histone deacetylase 2; DNA segment, Chr 10, Wayne State University 179, expressed [Mus musculus]
HG1000173N0_20000_gene_prediction1	gi 26345110 dbj BAC36204.1  unnamed protein product [Mus musculus]
HG1000834N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001044N0_1000_gene_prediction1	gi 26330836 dbj BAC29148.1  unnamed protein product [Mus musculus]
HG1000299N0_1000_gene_prediction1	gi 6753882 ref NP_034349.1  FK506 binding protein 4 (59 kDa) [Mus musculus]
HG1000752N0_10000_gene_prediction1	gi 25955698 gb AAH40387.1  Similar to PTPL1-associated RhoGAP 1 [Mus musculus]
HG1000839N0_160000_gene_prediction2	gi 17512422 gb AAH19171.1  Similar to RIKEN cDNA 2310010G13 gene [Mus musculus]
HG1000659N0_160000_gene_prediction1	gi 26333733 dbj BAC30584.1  unnamed protein product [Mus musculus]
HG1000659N0_160000_gene_prediction2	gi 26333733 dbj BAC30584.1  unnamed protein product [Mus musculus]
HG1000013N0_160000_gene_prediction1	gi 20881136 ref XP_126284.1  similar to sperm antigen HCMOGT-1 [Homo sapiens] [Mus

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
	musculus]
HG1000173N0_160000_gene_prediction1	gi 26345110 dbj BAC36204.1  unnamed protein product [Mus musculus]
HG1000330N0_160000_gene_prediction1	gi 27462832 gb AAO15605.1 AF462146_1 modulator of estrogen induced transcription [Mus musculus]
HG1000360N0_20000_gene_prediction1	gi 7861746 gb AAF70384.1 AF189263_1 GABA-A receptor epsilon-like subunit [Mus musculus]
HG1000178N0_10000_gene_prediction1	gi 13384830 ref NP_079706.1  RIKEN cDNA 1110066C01 [Mus musculus]
HG1000178N0_10000_gene_prediction2	gi 13384830 ref NP_079706.1  RIKEN cDNA 1110066C01 [Mus musculus]
HG1000360N0_20000_gene_prediction2	gi 7861746 gb AAF70384.1 AF189263_1 GABA-A receptor epsilon-like subunit [Mus musculus]
HG1000640N0_160000_gene_prediction1	gi 21313034 ref NP_080346.1  RIKEN cDNA 2900091E11 [Mus musculus]
HG1001000N0_160000_gene_prediction1	gi 10181212 ref NP_065613.1  RIKEN cDNA 1300007B12; clone MNCb-2755 [Mus musculus]
HG1001418N0_160000_gene_prediction1	gi 20819462 ref XP_158058.1  hypothetical protein XP_158058 [Mus musculus]
HG1000153N0_20000_gene_prediction1	gi 26379523 dbj BAB29070.2  unnamed protein product [Mus musculus]
HG1000255N0_160000_gene_prediction1	gi 13385532 ref NP_080303.1  RIKEN cDNA 2700086I23 [Mus musculus]
HG1000186N0_160000_gene_prediction1	gi 20963196 ref XP_135684.1  RIKEN cDNA 1700022L20 [Mus musculus]
HG1000259N0_160000_gene_prediction1	gi 26360198 dbj BAB25612.2  unnamed protein product [Mus musculus]
HG1000559N0_10000_gene_prediction1	
HG1000084N0_10000_gene_prediction1	gi 6678794 ref NP_032953.1  mitogen activated protein kinase kinase 1; MAP kinase kinase 1; protein kinase, mitogen activated, kinase 1, p45 [Mus musculus]
HG1000217N0_160000_gene_prediction1	gi 6681015 ref NP_031789.1  cysteine rich intestinal protein [Mus musculus]
HG1000217N0_160000_gene_prediction2	gi 6681015 ref NP_031789.1  cysteine rich intestinal protein [Mus musculus]
HG1000329N0_160000_gene_prediction1	gi 26330870 dbj BAC29165.1  unnamed protein product [Mus musculus]
HG1000570N0_160000_gene_prediction1	gi 6716522 gb AAF26675.1 AF155821_1

FP ID	Fantom Top Hit Annotation
n1	CPG16 [Mus musculus]
HG1000617N0_40000_gene_prediction 1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000227N0_160000_gene_predictio n1	gi 21362402 sp Q9CZB0 C560_MOUSE Succinate dehydrogenase cytochrome b560 subunit, mitochondrial precursor (Integral membrane protein CII-3) (QPS1) (QPs-1)
HG1000269N0_10000_gene_prediction 1	gi 7706341 ref NP_057145.1  yippee protein [Homo sapiens]
HG1000615N0_160000_gene_prediction n2	gi 4506725 ref NP_000998.1  ribosomal protein S4, X-linked X isoform; 40S ribosomal protein S4, X isoform; ribosomal protein S4X isoform; single-copy abundant mRNA; cell cycle gene 2 [Homo sapiens]
HG1000617N0_160000_gene_predictio n1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000621N0_160000_gene_predictio n2	gi 4506725 ref NP_000998.1  ribosomal protein S4, X-linked X isoform; 40S ribosomal protein S4, X isoform; ribosomal protein S4X isoform; single-copy abundant mRNA; cell cycle gene 2 [Homo sapiens]
HG1000990N0_160000_gene_predictio n1	gi 10946760 ref NP_067381.1  triggering receptor expressed on myeloid cells 1; triggering receptor expressed in monocytes 1 [Mus musculus]
HG1000998N0_160000_gene_predictio n1	gi 6678483 ref NP_033483.1  ubiquitin- activating enzyme E1, Chr X [Mus musculus]
HG1001225N0_160000_gene_predictio n1	gi 10181192 ref NP_065589.1  sulfotransferase- related protein SULT-X1 [Mus musculus]
HG1001269N0_5000_gene_prediction1	gi 21311883 ref NP_080887.1  RIKEN cDNA 0610007O07 [Mus musculus]
HG1001269N0_160000_gene_predictio n1	gi 21311883 ref NP_080887.1  RIKEN cDNA 0610007O07 [Mus musculus]
HG1000103N0_160000_gene_predictio n1	gi 26327721 dbj BAC27604.1  unnamed protein product [Mus musculus]
HG1000143N0_1000_gene_prediction1	gi 14141193 ref NP_001004.2  ribosomal protein S9; 40S ribosomal protein S9 [Homo sapiens]
HG1000396N0_160000_gene_predictio n1	gi 25024769 ref XP_207136.1  similar to ORF2 [Mus musculus domesticus]
HG1001502N0_160000_gene_predictio n2	gi 2144100 pir  I64837 Set beta isoform - rat
HG1000066N0_160000_gene_predictio n1	gi 26337951 dbj BAC32661.1  unnamed protein product [Mus musculus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000078N0_1000_gene_prediction1	gi 26346587 dbj BAC36942.1  unnamed protein product [Mus musculus]
HG1000117N0_160000_gene_prediction1	gi 20875580 ref XP_131162.1  sorting nexin 7 [Mus musculus]
HG1000157N0_160000_gene_prediction1	gi 26344914 dbj BAC36106.1  unnamed protein product [Mus musculus]
HG1000194N0_160000_gene_prediction1	gi 21313022 ref NP_083674.1  RIKEN cDNA 5730496E24 [Mus musculus]
HG1000501N0_160000_gene_prediction1	gi 27370478 ref NP_766552.1  hypothetical protein E130310N06 [Mus musculus]
HG1000656N0_10000_gene_prediction1	gi 12855078 dbj BAB30210.1  unnamed protein product [Mus musculus]
HG1000656N0_10000_gene_prediction2	gi 12855078 dbj BAB30210.1  unnamed protein product [Mus musculus]
HG1000750N0_160000_gene_prediction1	gi 26336392 dbj BAC31881.1  unnamed protein product [Mus musculus]
HG1001012N0_160000_gene_prediction1	gi 21312504 ref NP_081554.1  RIKEN cDNA 2810432D09 [Mus musculus]
HG1001237N0_10000_gene_prediction1	gi 20882986 ref XP_126218.1  similar to Hermansky-Pudlak syndrome protein variant [Rattus norvegicus] [Mus musculus]
HG1000228N0_40000_gene_prediction1	gi 26342390 dbj BAC34857.1  unnamed protein product [Mus musculus]
HG1000228N0_20000_gene_prediction1	gi 13507676 ref NP_109647.1  pumilio 1 (Drosophila) [Mus musculus]
HG1000228N0_160000_gene_prediction1	gi 13507676 ref NP_109647.1  pumilio 1 (Drosophila) [Mus musculus]
HG1000390N0_160000_gene_prediction1	gi 20892585 ref XP_147977.1  RIKEN cDNA 2610001E17 [Mus musculus]
HG1000409N0_10000_gene_prediction1	gi 26006245 dbj BAC41465.1  mKIAA1047 protein [Mus musculus]
HG1000611N0_160000_gene_prediction1	gi 6650539 gb AAE21895.1 AF103877_1 epsilon-sarcoglycan [Mus musculus]
HG1000847N0_10000_gene_prediction1	
HG1000015N0_0_gene_prediction1	gi 20467423 ref NP_620570.1  chondroitin sulfate proteoglycan 4 [Mus musculus]
HG1000088N0_5000_gene_prediction1	gi 16741633 gb AAH16619.1  pyruvate kinase 3 [Mus musculus]
HG1000143N0_10000_gene_prediction1	gi 20896345 ref XP_128324.1  carbonyl reductase 3 [Mus musculus]
HG1000167N0_5000_gene_prediction1	gi 12848663 dbj BAB28043.1  unnamed protein product [Mus musculus]

177

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
n1	product [Mus musculus]
HG1000187N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000247N0_160000_gene_prediction1	gi 7656920 ref NP_056547.1  axin2 [Mus musculus]
HG1000273N0_160000_gene_prediction2	gi 25030042 ref XP_207307.1  similar to Retrovirus-related POL polypotein [Mus musculus]
HG1000415N0_10000_gene_prediction1	gi 9367840 emb CAB97523.1  hypothetical protein, weakly similar to (AF102871) neuronal apoptosis inhibitory protein 2 [Mus musculus] [Homo sapiens]
HG1000539N0_160000_gene_prediction1	gi 7521942 pir T29096 gag polyprotein - murine endogenous retrovirus ERV-L
HG1000539N0_160000_gene_prediction2	gi 7521942 pir T29096 gag polyprotein - murine endogenous retrovirus ERV-L
HG1000560N0_160000_gene_prediction1	gi 12860683 dbj BAB32021.1  unnamed protein product [Mus musculus]
HG1000618N0_10000_gene_prediction1	gi 26350749 dbj BAC3901.1  unnamed protein product [Mus musculus]
HG1000740N0_160000_gene_prediction1	gi 23601536 ref XP_130965.2  Nice-4 protein homolog [Mus musculus]
HG1001197N0_160000_gene_prediction1	gi 26327779 dbj BAC27630.1  unnamed protein product [Mus musculus]
HG1000599N0_5000_gene_prediction1	gi 12836542 dbj BAB23701.1  unnamed protein product [Mus musculus]
HG1000020N0_5000_gene_prediction1	gi 20887101 ref XP_129228.1  similar to phosphoglucomutase 5 [Homo sapiens] [Mus musculus]
HG1000084N0_5000_gene_prediction1	gi 6678794 ref NP_032953.1  mitogen activated protein kinase kinase 1; MAP kinase kinase 1; protein kinase, mitogen activated, kinase 1, p45 [Mus musculus]
HG1000135N0_5000_gene_prediction1	gi 21312189 ref NP_081197.1  RIKEN cDNA 1810010A06 [Mus musculus]
HG1000169N0_20000_gene_prediction1	gi 20886743 ref XP_129211.1  phosphoserine aminotransferase [Mus musculus]
HG1000169N0_160000_gene_prediction1	gi 20886743 ref XP_129211.1  phosphoserine aminotransferase [Mus musculus]
HG1000189N0_160000_gene_prediction1	gi 20879992 ref XP_140210.1  similar to BG:DS01759.1 gene product [Drosophila melanogaster] [Mus musculus]
HG1000189N0_160000_gene_prediction2	gi 20879992 ref XP_140210.1  similar to BG:DS01759.1 gene product [Drosophila

FP ID	Fantom Top Hit Annotation
	melanogaster] [Mus musculus]
HG1000246N0_5000_gene_prediction1	gi 21450297 ref NP_659157.1  UDP-GalNAc:polypeptide N-acetyl-galactosaminyltransferase [Mus musculus]
HG1000248N0_0_gene_prediction1	gi 9790219 ref NP_062745.1  destrin; Sid23p [Mus musculus]
HG1000288N0_10000_gene_prediction1	gi 20909512 ref XP_153447.1  hypothetical protein XP_153447 [Mus musculus]
HG1000424N0_5000_gene_prediction1	gi 25031822 ref XP_207741.1  hypothetical protein XP_207741 [Mus musculus]
HG1000443N0_40000_gene_prediction1	gi 26354072 dbj BAC40666.1  unnamed protein product [Mus musculus]
HG1000590N0_1000_gene_prediction1	gi 26378096 dbj BAB28595.2  unnamed protein product [Mus musculus]
HG1000626N0_160000_gene_prediction1	gi 9938030 ref NP_064667.1  hypothetical protein, MNCb-4I93; hypothetical protein MNCb-4I93 [Mus musculus]
HG1000871N0_160000_gene_prediction1	gi 6752958 ref NP_033742.1  activin A receptor, type II-like 1; activin receptor-like kinase-1 [Mus musculus]
HG1000959N0_10000_gene_prediction1	gi 22507385 ref NP_081019.1  RIKEN cDNA 1110014F12 [Mus musculus]
HG1000961N0_160000_gene_prediction3	gi 20822904 ref XP_131914.1  RIKEN cDNA 3110004O18 [Mus musculus]
HG1000974N0_5000_gene_prediction1	gi 26378096 dbj BAB28595.2  unnamed protein product [Mus musculus]
HG1001045N0_160000_gene_prediction1	gi 25020138 ref XP_207789.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
HG1001110N0_0_gene_prediction1	gi 23956080 ref NP_058675.1  putative serine/threonine kinase [Mus musculus]
HG1001223N0_1000_gene_prediction1	gi 26339658 dbj BAC33500.1  unnamed protein product [Mus musculus]
HG1001281N0_160000_gene_prediction1	gi 15431279 ref NP_203538.1  dedicator of cyto-kinesis 2 [Mus musculus]
HG1001317N0_5000_gene_prediction1	gi 26327365 dbj BAC27426.1  unnamed protein product [Mus musculus]
HG1001485N0_5000_gene_prediction1	gi 26327365 dbj BAC27426.1  unnamed protein product [Mus musculus]
HG1000674N0_160000_gene_prediction1	gi 24211881 sp Q8VCR8 KML2_MOUSE Myosin light chain kinase 2, skeletal/cardiac muscle (MLCK2)
HG1001017N0_10000_gene_prediction	gi 25019831 ref XP_207463.1  similar to



WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
1	CD59B [Mus musculus]
HG1001017N0_1000_gene_prediction1	gi 25019831 ref XP_207463.1  similar to CD59B [Mus musculus]
HG1000014N0_160000_gene_prediction2	gi 6680744 ref NP_031528.1  ATPase, Na+/K+ transporting, beta 3 polypeptide; ATPase, Na+/K+ beta 3 polypeptide [Mus musculus]
HG1000043N0_160000_gene_prediction3	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1000052N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000084N0_5000_gene_prediction2	gi 6678794 ref NP_032953.1  mitogen activated protein kinase kinase 1; MAP kinase kinase 1; protein kinase, mitogen activated, kinase 1, p45 [Mus musculus]
HG1000093N0_1000_gene_prediction1	gi 26350865 dbj BAC39069.1  unnamed protein product [Mus musculus]
HG1000105N0_160000_gene_prediction1	gi 14198371 gb AAH08247.1  Similar to cyclin B2 [Mus musculus]
HG1000157N0_1000_gene_prediction1	gi 5803225 ref NP_006752.1  tyrosine 3/tryptophan 5 -monooxygenase activation protein, epsilon polypeptide; 14-3-3 epsilon; mitochondrial import stimulation factor L subunit; protein kinase C inhibitor protein-1 [Homo sapiens]
HG1000210N0_40000_gene_prediction1	gi 17160840 gb AAH17597.1  RIKEN cDNA 5830401B18 gene [Mus musculus]
HG1000242N0_5000_gene_prediction1	gi 9789937 ref NP_062768.1  DnaJ (Hsp40) homolog, subfamily A, member 2; DNA J protein [Mus musculus]
HG1000243N0_5000_gene_prediction2	gi 8393534 ref NP_058653.1  high mobility group protein 17 [Mus musculus]
HG1000256N0_160000_gene_prediction1	gi 13959400 sp Q9R0Y5 KAD1_MOUSE Adenylate kinase isoenzyme 1 (ATP-AMP transphosphorylase) (AK1) (Myokinase)
HG1000279N0_0_gene_prediction1	gi 15617203 ref NP_254279.1  chloride intracellular channel 1 [Mus musculus]
HG1000280N0_5000_gene_prediction1	gi 7106337 ref NP_034796.1  keratin complex-1, gene C29 [Mus musculus]
HG1000280N0_5000_gene_prediction2	gi 7106337 ref NP_034796.1  keratin complex-1, gene C29 [Mus musculus]
HG1000282N0_160000_gene_prediction1	gi 20902823 ref XP_128021.1  similar to Mitochondrial import receptor subunit TOM22 homolog (Translocase of outer membrane 22 kDa subunit homolog) (hTom22) (IC9-2) [Mus musculus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000292N0_160000_gene_prediction1	gi 6981488 ref NP_037356.1  ribosomal protein S26 [Rattus norvegicus]
HG1000313N0_160000_gene_prediction1	gi 4506283 ref NP_003454.1  protein tyrosine phosphatase type IVA, member 1; Protein tyrosine phosphatase IVA1 [Homo sapiens]
HG1000330N0_20000_gene_prediction1	gi 22122511 ref NP_666146.1  hypothetical protein MGC30562 [Mus musculus]
HG1000339N0_160000_gene_prediction1	gi 26350551 dbj BAC38915.1  unnamed protein product [Mus musculus]
HG1000340N0_160000_gene_prediction1	gi 20912842 ref XP_126689.1  RIKEN cDNA 3300001P08 [Mus musculus]
HG1000344N0_160000_gene_prediction1	gi 21450239 ref NP_659092.1  hypothetical protein MGC27983 [Mus musculus]
HG1000365N0_20000_gene_prediction1	gi 25046794 ref XP_207489.1  similar to RNP particle component [Mus musculus]
HG1000384N0_160000_gene_prediction1	gi 20909520 ref XP_126941.1  RIKEN cDNA 2600011C06 [Mus musculus]
HG1000448N0_160000_gene_prediction1	gi 6678247 ref NP_033358.1  transcription factor 7-like 1 [Mus musculus]
HG1000482N0_160000_gene_prediction1	gi 26334795 dbj BAC31098.1  unnamed protein product [Mus musculus]
HG1000486N0_20000_gene_prediction1	gi 26350551 dbj BAC38915.1  unnamed protein product [Mus musculus]
HG1000506N0_160000_gene_prediction1	gi 20909520 ref XP_126941.1  RIKEN cDNA 2600011C06 [Mus musculus]
HG1000518N0_160000_gene_prediction1	gi 26351279 dbj BAC39276.1  unnamed protein product [Mus musculus]
HG1000550N0_160000_gene_prediction1	gi 20909520 ref XP_126941.1  RIKEN cDNA 2600011C06 [Mus musculus]
HG1000556N0_160000_gene_prediction1	gi 25031497 ref XP_207552.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
HG1000588N0_160000_gene_prediction1	gi 13277747 gb AAH03768.1  interferon-induced protein with tetratricopeptide repeats 1 [Mus musculus]
HG1000600N0_160000_gene_prediction1	gi 20863376 ref XP_134148.1  similar to hypothetical protein [Macaca fascicularis] [Mus musculus]
HG1000647N0_160000_gene_prediction1	gi 9506517 ref NP_062338.1  cytotoxic and regulatory T cell molecule; class I-restricted T cell-associated molecule [Mus musculus]
HG1000648N0_160000_gene_prediction1	gi 20900199 ref XP_128639.1  RIKEN cDNA 2810055C19 [Mus musculus]
HG1000688N0_160000_gene_prediction1	gi 26327707 dbj BAC27597.1  unnamed protein

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
n1	product [Mus musculus]
HG1000696N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000788N0_160000_gene_prediction1	gi 20847912 ref XP_144610.1  similar to KIAA1904 protein [Homo sapiens] [Mus musculus]
HG1000874N0_160000_gene_prediction1	gi 20342176 ref XP_110490.1  similar to hypothetical protein MGC955 [Homo sapiens] [Mus musculus]
HG1000902N0_20000_gene_prediction1	gi 6753324 ref NP_033968.1  chaperonin subunit 6a (zeta); chaperonin containing TCP-1 [Mus musculus]
HG1000902N0_160000_gene_prediction2	gi 6753324 ref NP_033968.1  chaperonin subunit 6a (zeta); chaperonin containing TCP-1 [Mus musculus]
HG1000902N0_1000_gene_prediction1	gi 6753324 ref NP_033968.1  chaperonin subunit 6a (zeta); chaperonin containing TCP-1 [Mus musculus]
HG1000904N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000966N0_1000_gene_prediction1	gi 22122617 ref NP_666215.1  hypothetical protein MGC25511 [Mus musculus]
HG1000966N0_5000_gene_prediction1	gi 22122617 ref NP_666215.1  hypothetical protein MGC25511 [Mus musculus]
HG1000994N0_160000_gene_prediction1	gi 12855175 dbj BAB30238.1  unnamed protein product [Mus musculus]
HG1001014N0_160000_gene_prediction3	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1001041N0_5000_gene_prediction1	gi 25071304 ref XP_146497.3  similar to protein serine kinase Pskh1 [Mus musculus]
HG1001337N0_160000_gene_prediction1	gi 27369704 ref NP_766096.1  hypothetical protein 6030499O08 [Mus musculus]
HG1001417N0_5000_gene_prediction1	gi 26349767 dbj BAC38523.1  unnamed protein product [Mus musculus]
HG1001485N0_160000_gene_prediction1	gi 7513636 pir T30805 dutt1 protein - mouse
HG1000151N0_160000_gene_prediction1	gi 18044328 gb AAH19573.1  Unknown (protein for IMAGE:3990036) [Mus musculus]
HG1000330N0_160000_gene_prediction3	gi 25029811 ref XP_207217.1  similar to ORF2 [Mus musculus domesticus]
HG1000957N0_20000_gene_prediction1	gi 25024769 ref XP_207136.1  similar to ORF2 [Mus musculus domesticus]
HG1000960N0_0_gene_prediction1	gi 20908689 ref XP_127449.1  RIKEN cDNA 4632401C08 [Mus musculus]

FP ID	Fantom Top Hit Annotation
HG1000960N0_0_gene_prediction2	gi 20908689 ref XP_127449.1  RIKEN cDNA 4632401C08 [Mus musculus]
HG1001280N0_20000_gene_prediction1	gi 26336763 dbj BAC32064.1  unnamed protein product [Mus musculus]
HG1001502N0_160000_gene_prediction1	gi 27370240 ref NP_766415.1  hypothetical protein 4732490P18 [Mus musculus]
HG1000003N0_10000_gene_prediction1	gi 13624305 ref NP_112440.1  procollagen, type II, alpha 1 [Mus musculus]
HG1000041N0_160000_gene_prediction1	gi 26390169 dbj BAC25854.1  unnamed protein product [Mus musculus]
HG1000043N0_160000_gene_prediction2	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1000044N0_5000_gene_prediction1	gi 15079309 gb AAH11494.1  Similar to Myosin of the dilute-myosin-V family [Mus musculus]
HG1000051N0_160000_gene_prediction1	gi 14250190 gb AAH08515.1  interferon regulatory factor 6 [Mus musculus]
HG1000057N0_160000_gene_prediction1	gi 6755040 ref NP_035202.1  profilin 1; actin binding protein [Mus musculus]
HG1000060N0_160000_gene_prediction1	gi 6755901 ref NP_035783.1  tubulin, alpha 1; tubulin alpha 1 [Mus musculus]
HG1000061N0_10000_gene_prediction1	gi 20827552 ref XP_130234.1  expressed sequence AW610751 [Mus musculus]
HG1000079N0_160000_gene_prediction1	gi 20887309 ref XP_129200.1  adenylate kinase 3 alpha like [Mus musculus]
HG1000098N0_160000_gene_prediction1	gi 26340666 dbj BAC33995.1  unnamed protein product [Mus musculus]
HG1000105N0_5000_gene_prediction1	gi 12850600 dbj BAB28785.1  unnamed protein product [Mus musculus]
HG1000121N0_160000_gene_prediction1	gi 26346402 dbj BAC36852.1  unnamed protein product [Mus musculus]
HG1000131N0_160000_gene_prediction1	gi 26329183 dbj BAC28330.1  unnamed protein product [Mus musculus]
HG1000134N0_160000_gene_prediction1	gi 12860377 dbj BAB31934.1  unnamed protein product [Mus musculus]
HG1000134N0_160000_gene_prediction2	gi 12860377 dbj BAB31934.1  unnamed protein product [Mus musculus]
HG1000136N0_160000_gene_prediction1	gi 26389519 dbj BAC25745.1  unnamed protein product [Mus musculus]
HG1000147N0_160000_gene_prediction1	gi 3717978 emb CAA73041.1  5S ribosomal protein [Mus musculus]
HG1000166N0_160000_gene_prediction1	gi 20908717 ref XP_127445.1  similar to flavoprotein subunit of succinate-ubiquinone reductase [Rattus norvegicus] [Mus musculus]

FP ID	Fantom Top Hit Annotation
HG1000172N0_1000_gene_prediction1	gi 6681095 ref NP_031834.1  cytochrome c, somatic [Mus musculus]
HG1000172N0_1000_gene_prediction2	gi 6681095 ref NP_031834.1  cytochrome c, somatic [Mus musculus]
HG1000175N0_5000_gene_prediction1	gi 26354216 dbj BAC40736.1  unnamed protein product [Mus musculus]
HG1000175N0_10000_gene_prediction1	gi 26354216 dbj BAC40736.1  unnamed protein product [Mus musculus]
HG1000175N0_160000_gene_prediction1	gi 26354216 dbj BAC40736.1  unnamed protein product [Mus musculus]
HG1000175N0_1000_gene_prediction1	gi 26354216 dbj BAC40736.1  unnamed protein product [Mus musculus]
HG1000192N0_160000_gene_prediction1	gi 10946614 ref NP_067287.1  WD repeat domain 12; nuclear protein Ytm1 [Mus musculus]
HG1000193N0_160000_gene_prediction2	gi 21728370 ref NP_080178.1  RIKEN cDNA 1500009M05 [Mus musculus]
HG1000195N0_160000_gene_prediction1	gi 17390530 gb AAH18231.1  Unknown (protein for MGC:19236) [Mus musculus]
HG1000197N0_160000_gene_prediction1	gi 21450185 ref NP_659063.1  hypothetical protein MGC28186 [Mus musculus]
HG1000202N0_20000_gene_prediction1	gi 26331946 dbj BAC29703.1  unnamed protein product [Mus musculus]
HG1000210N0_20000_gene_prediction1	gi 17160840 gb AAH17597.1  RIKEN cDNA 5830401B18 gene [Mus musculus]
HG1000218N0_1000_gene_prediction1	gi 6681015 ref NP_031789.1  cysteine rich intestinal protein [Mus musculus]
HG1000218N0_160000_gene_prediction1	gi 6681015 ref NP_031789.1  cysteine rich intestinal protein [Mus musculus]
HG1000218N0_10000_gene_prediction1	gi 6681015 ref NP_031789.1  cysteine rich intestinal protein [Mus musculus]
HG1000222N0_1000_gene_prediction1	gi 13385054 ref NP_079873.1  RIKEN cDNA 2700033I16 [Mus musculus]
HG1000233N0_1000_gene_prediction1	gi 12847362 dbj BAB27541.1  unnamed protein product [Mus musculus]
HG1000234N0_1000_gene_prediction1	gi 12847362 dbj BAB27541.1  unnamed protein product [Mus musculus]
HG1000234N0_160000_gene_prediction1	gi 12847362 dbj BAB27541.1  unnamed protein product [Mus musculus]
HG1000238N0_160000_gene_prediction2	gi 6671549 ref NP_031479.1  anti-oxidant protein 2; acidic calcium-independent phospholipase A2; peroxiredoxin 5; 1-Cys Prx [Mus musculus]
HG1000240N0_160000_gene_prediction1	gi 26328673 dbj BAC28075.1  unnamed protein

FP ID	Fantom Top Hit Annotation
n1	product [Mus musculus]
HG1000245N0_160000_gene_prediction1	gi 12850132 dbj BAB28604.1  unnamed protein product [Mus musculus]
HG1000245N0_5000_gene_prediction1	gi 12850132 dbj BAB28604.1  unnamed protein product [Mus musculus]
HG1000249N0_10000_gene_prediction1	gi 6754654 ref NP_034905.1  mannose binding lectin, liver (A) [Mus musculus]
HG1000251N0_160000_gene_prediction1	gi 20881913 ref XP_126211.1  Dullard homolog [Mus musculus]
HG1000252N0_5000_gene_prediction1	gi 20825536 ref XP_129507.1  ring finger protein 2 [Mus musculus]
HG1000254N0_160000_gene_prediction1	gi 13385058 ref NP_079878.1  hypothetical protein D10Erd718e [Mus musculus]
HG1000262N0_160000_gene_prediction1	gi 21312163 ref NP_082683.1  RIKEN cDNA 2900054P12 [Mus musculus]
HG1000264N0_1000_gene_prediction1	gi 21624617 ref NP_081018.1  RIKEN cDNA 1110007M04 [Mus musculus]
HG1000264N0_1000_gene_prediction2	gi 21624617 ref NP_081018.1  RIKEN cDNA 1110007M04 [Mus musculus]
HG1000270N0_20000_gene_prediction1	gi 12844196 dbj BAB26273.1  unnamed protein product [Mus musculus]
HG1000270N0_1000_gene_prediction1	gi 12852884 dbj BAB29566.1  unnamed protein product [Mus musculus]
HG1000274N0_160000_gene_prediction1	gi 26347831 dbj BAC37564.1  unnamed protein product [Mus musculus]
HG1000276N0_160000_gene_prediction1	gi 19527228 ref NP_598768.1  DNA segment, Chr 10, ERATO Doi 214, expressed [Mus musculus]
HG1000276N0_5000_gene_prediction1	gi 19527228 ref NP_598768.1  DNA segment, Chr 10, ERATO Doi 214, expressed [Mus musculus]
HG1000278N0_5000_gene_prediction1	gi 19527026 ref NP_598568.1  expressed sequence AA959742 [Mus musculus]
HG1000280N0_160000_gene_prediction1	gi 7106337 ref NP_034796.1  keratin complex-1, gene C29 [Mus musculus]
HG1000280N0_1000_gene_prediction1	gi 7106337 ref NP_034796.1  keratin complex-1, gene C29 [Mus musculus]
HG1000280N0_160000_gene_prediction2	gi 7106337 ref NP_034796.1  keratin complex-1, gene C29 [Mus musculus]
HG1000280N0_1000_gene_prediction2	gi 7106337 ref NP_034796.1  keratin complex-1, gene C29 [Mus musculus]
HG1000305N0_5000_gene_prediction1	gi 27369902 ref NP_766218.1  hypothetical protein A530095G11 [Mus musculus]

186

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
	nuclear regulator; TATA box binding protein (TBP)-associated factor, RNA polymerase III, GTF3B subunit 1; ... [Mus musculus]
HG1000457N0_160000_gene_prediction1	gi 20824761 ref XP_133346.1  liver-specific bHLH-Zip transcription factor [Mus musculus]
HG1000458N0_160000_gene_prediction1	gi 12841242 dbj BAB25129.1  unnamed protein product [Mus musculus]
HG1000461N0_160000_gene_prediction1	gi 25032310 ref XP_205729.1  hypothetical protein XP_205729 [Mus musculus]
HG1000463N0_160000_gene_prediction1	gi 12861068 dbj BAB32114.1  unnamed protein product [Mus musculus]
HG1000463N0_160000_gene_prediction2	gi 13249351 ref NP_076402.1  inositol-requiring 1 alpha (yeast) [Mus musculus]
HG1000476N0_160000_gene_prediction1	gi 26332657 dbj BAC30046.1  unnamed protein product [Mus musculus]
HG1000481N0_160000_gene_prediction1	gi 21311873 ref NP_077181.1  RIKEN cDNA 0610007A03 [Mus musculus]
HG1000530N0_160000_gene_prediction1	gi 20860491 ref XP_153755.1  hypothetical protein XP_153755 [Mus musculus]
HG1000556N0_160000_gene_prediction2	gi 25031497 ref XP_207552.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
HG1000584N0_160000_gene_prediction1	gi 27370500 ref NP_766581.1  hypothetical protein D230008H22 [Mus musculus]
HG1000587N0_160000_gene_prediction1	gi 23682449 ref XP_158842.2  hypothetical protein XP_158842 [Mus musculus]
HG1000592N0_160000_gene_prediction1	gi 26349599 dbj BAC38439.1  unnamed protein product [Mus musculus]
HG1000594N0_160000_gene_prediction1	gi 22095015 ref NP_084065.1  RIKEN cDNA 0610013I17 [Mus musculus]
HG1000594N0_160000_gene_prediction2	gi 22095015 ref NP_084065.1  RIKEN cDNA 0610013I17 [Mus musculus]
HG1000608N0_160000_gene_prediction1	gi 20345223 ref XP_109778.1  similar to Neurabin-II (Neural tissue-specific F-actin binding protein II) (Protein phosphatase 1 regulatory subunit 9B) (Spinophilin) (p130) (PP1bp134) [Mus musculus]
HG1000615N0_160000_gene_prediction1	gi 7710032 ref NP_057928.1  growth factor receptor bound protein 14 [Mus musculus]
HG1000620N0_160000_gene_prediction1	gi 25052462 ref XP_138105.3  similar to TAR DNA-binding protein-43 (TDP-43) [Mus musculus]
HG1000621N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]



WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000621N0_160000_gene_prediction3	gi 26382861 dbj BAC25510.1  unnamed protein product [Mus musculus]
HG1000631N0_40000_gene_prediction1	gi 6681283 ref NP_031938.1  epidermal growth factor receptor; avian erythroblastic leukemia viral (v-erb-b) oncogene homolog [Mus musculus]
HG1000652N0_160000_gene_prediction1	gi 25030122 ref XP_207332.1  similar to endonuclease/reverse transcriptase [Mus musculus]
HG1000663N0_160000_gene_prediction1	gi 20915416 ref XP_162987.1  hypothetical protein XP_162987 [Mus musculus]
HG1000686N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000700N0_160000_gene_prediction1	gi 16508047 gb AAL17972.1  pORF2 [Mus musculus domesticus]
HG1000701N0_160000_gene_prediction1	gi 26327167 dbj BAC27327.1  unnamed protein product [Mus musculus]
HG1000709N0_160000_gene_prediction1	gi 220579 dbj BAA00448.1  open reading frame (196 AA) [Mus musculus]
HG1000712N0_160000_gene_prediction1	gi 12841826 dbj BAB25366.1  unnamed protein product [Mus musculus]
HG1000720N0_160000_gene_prediction1	gi 7657415 ref NP_035986.2  odd Oz/ten-m homolog 2 (Drosophila); odd Oz/ten-m homolog 3 (Drosophila) [Mus musculus]
HG1000727N0_160000_gene_prediction1	gi 26335645 dbj BAC31523.1  unnamed protein product [Mus musculus]
HG1000743N0_160000_gene_prediction2	gi 26338834 dbj BAC33088.1  unnamed protein product [Mus musculus]
HG1000767N0_5000_gene_prediction1	gi 12851918 dbj BAB29207.1  unnamed protein product [Mus musculus]
HG1000786N0_160000_gene_prediction2	gi 6678303 ref NP_033386.1  transcription factor A, mitochondrial [Mus musculus]
HG1000822N0_160000_gene_prediction1	gi 6680195 ref NP_032255.1  histone deacetylase 2; DNA segment, Chr 10, Wayne State University 179, expressed [Mus musculus]
HG1000829N0_160000_gene_prediction1	gi 21450159 ref NP_659049.1  cDNA sequence BC024131; hypothetical protein MGC37896 [Mus musculus]
HG1000848N0_160000_gene_prediction1	gi 26350995 dbj BAC39134.1  unnamed protein product [Mus musculus]
HG1000860N0_160000_gene_prediction1	gi 26325678 dbj BAC26593.1  unnamed protein product [Mus musculus]
HG1000898N0_10000_gene_prediction	gi 21450209 ref NP_659075.1  hypothetical

FP ID	Fantom Top Hit Annotation
l	protein MGC25509 [Mus musculus]
HG1000898N0_160000_gene_prediction1	gi 21450209 ref NP_659075.1  hypothetical protein MGC25509 [Mus musculus]
HG1000898N0_200000_gene_prediction1	gi 21450209 ref NP_659075.1  hypothetical protein MGC25509 [Mus musculus]
HG1000902N0_160000_gene_prediction1	gi 21450209 ref NP_659075.1  hypothetical protein MGC25509 [Mus musculus]
HG1000904N0_160000_gene_prediction3	gi 6753324 ref NP_033968.1  chaperonin subunit 6a (zeta); chaperonin containing TCP-1 [Mus musculus]
HG1000906N0_200000_gene_prediction1	gi 20344324 ref XP_109683.1  RIKEN cDNA 1810027O10 [Mus musculus]
HG1000906N0_160000_gene_prediction1	gi 26346114 dbj BAC36708.1  unnamed protein product [Mus musculus]
HG1000921N0_5000_gene_prediction1	gi 26346114 dbj BAC36708.1  unnamed protein product [Mus musculus]
HG1000938N0_100000_gene_prediction1	gi 26350775 dbj BAC39024.1  unnamed protein product [Mus musculus]
HG1000952N0_160000_gene_prediction1	gi 26339054 dbj BAC33198.1  unnamed protein product [Mus musculus]
HG1000961N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000961N0_160000_gene_prediction2	gi 25051287 ref XP_146665.3  similar to KIAA0877 protein [Homo sapiens] [Mus musculus]
HG1001000N0_160000_gene_prediction2	gi 20859143 ref XP_127126.1  similar to eukaryotic initiation factor 5 [Rattus norvegicus] [Mus musculus]
HG1001003N0_160000_gene_prediction1	gi 19527072 ref NP_598613.1  expressed sequence AW555139 [Mus musculus]
HG1001007N0_160000_gene_prediction1	gi 13277825 gb AAH03796.1  Similar to lymphocyte specific 1 [Mus musculus]
HG1001009N0_0_gene_prediction1	gi 26334641 dbj BAC31021.1  unnamed protein product [Mus musculus]
HG1001014N0_160000_gene_prediction2	gi 26329567 dbj BAC28522.1  unnamed protein product [Mus musculus]
HG1001017N0_400000_gene_prediction1	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1001017N0_200000_gene_prediction1	gi 25019831 ref XP_207463.1  similar to CD59B [Mus musculus]
HG1001144N0_160000_gene_prediction1	gi 25019831 ref XP_207463.1  similar to CD59B [Mus musculus]
HG1001172N0_160000_gene_prediction2	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1001214N0_20000_gene_prediction1	gi 26340706 dbj BAC34015.1  unnamed protein product [Mus musculus]
HG1001229N0_160000_gene_prediction1	
HG1001253N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001253N0_160000_gene_prediction2	gi 26326251 dbj BAC26869.1  unnamed protein product [Mus musculus]
HG1001267N0_160000_gene_prediction1	gi 26326251 dbj BAC26869.1  unnamed protein product [Mus musculus]
HG1001289N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001343N0_10000_gene_prediction1	gi 26333317 dbj BAC30376.1  unnamed protein product [Mus musculus]
HG1001343N0_160000_gene_prediction1	gi 6755060 ref NP_035214.1  phosphatidylinositol 3-kinase, C2 domain containing, gamma polypeptide [Mus musculus]
HG1001390N0_160000_gene_prediction1	gi 6755060 ref NP_035214.1  phosphatidylinositol 3-kinase, C2 domain containing, gamma polypeptide [Mus musculus]
HG1001468N0_160000_gene_prediction1	gi 6680083 ref NP_032189.1  growth factor receptor bound protein 2 [Mus musculus]
HG1001508N0_160000_gene_prediction2	gi 25030495 ref XP_205178.1  similar to bA130N24.1 (nove) protein similar to REV3L (REV3 (yeast homolog)-like, catalytic subunit of DNA polymerase zeta) (POLZ)) [Homo sapiens] [Mus musculus]
HG1000084N0_160000_gene_prediction1	gi 26382861 dbj BAC25510.1  unnamed protein product [Mus musculus]
HG1000084N0_160000_gene_prediction2	gi 25031822 ref XP_207741.1  hypothetical protein XP_207741 [Mus musculus]
HG1000209N0_160000_gene_prediction1	gi 25031822 ref XP_207741.1  hypothetical protein XP_207741 [Mus musculus]
HG1000382N0_160000_gene_prediction1	gi 20858167 ref XP_125585.1  similar to PTD013 protein; CGI-24 protein [Mus musculus]
HG1000591N0_160000_gene_prediction1	gi 6678716 ref NP_032539.1  low density lipoprotein receptor-related protein 5; low density lipoprotein-related protein 5 [Mus musculus]
HG1000904N0_160000_gene_prediction4	gi 26330005 dbj BAC28741.1  unnamed protein product [Mus musculus]

FP ID	Fantom Top Hit Annotation
HG1000005N0_160000_gene_prediction1	gi 20835832 ref XP_129684.1  complement receptor 2 [Mus musculus]
HG1000014N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000015N0_160000_gene_prediction1	gi 6680744 ref NP_031528.1  ATPase, Na+/K+ transporting, beta 3 polypeptide; ATPase, Na+/K+ beta 3 polypeptide [Mus musculus]
HG1000015N0_20000_gene_prediction1	gi 20467423 ref NP_620570.1  chondroitin sulfate proteoglycan 4 [Mus musculus]
HG1000015N0_5000_gene_prediction1	gi 20467423 ref NP_620570.1  chondroitin sulfate proteoglycan 4 [Mus musculus]
HG1000015N0_160000_gene_prediction2	gi 20467423 ref NP_620570.1  chondroitin sulfate proteoglycan 4 [Mus musculus]
HG1000020N0_160000_gene_prediction1	gi 20467423 ref NP_620570.1  chondroitin sulfate proteoglycan 4 [Mus musculus]
HG1000020N0_5000_gene_prediction2	gi 26330706 dbj BAC29083.1  unnamed protein product [Mus musculus]
HG1000024N0_10000_gene_prediction1	gi 20887101 ref XP_129228.1  similar to phosphoglucomutase 5 [Homo sapiens] [Mus musculus]
HG1000026N0_160000_gene_prediction1	gi 12853786 dbj BAB29848.1  unnamed protein product [Mus musculus]
HG1000030N0_160000_gene_prediction1	gi 9506367 ref NP_062425.1  ATP-binding cassette, sub-family B, member 10; ATP-binding cassette, sub-family B (MDR/TAP), member 12; Abc-mitochondrial erythroid [Mus musculus]
HG1000039N0_160000_gene_prediction1	gi 26006203 dbj BAC41444.1  mKIAA0696 protein [Mus musculus]
HG1000041N0_5000_gene_prediction1	gi 7106453 ref NP_035897.1  zinc finger RNA binding protein [Mus musculus]
HG1000043N0_160000_gene_prediction1	gi 26390169 dbj BAC25854.1  unnamed protein product [Mus musculus]
HG1000043N0_5000_gene_prediction1	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1000044N0_20000_gene_prediction1	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1000052N0_160000_gene_prediction2	gi 15079309 gb AAH11494.1  Similar to Myosin of the dilute-myosin-V family [Mus musculus]
HG1000052N0_10000_gene_prediction1	gi 26324852 dbj BAC26180.1  unnamed protein product [Mus musculus]
HG1000052N0_20000_gene_prediction1	gi 26324852 dbj BAC26180.1  unnamed protein product [Mus musculus]

FP ID	Fantom Top Hit Annotation
HG1000058N0_10000_gene_prediction1	gi 26324852 dbj BAC26180.1  unnamed protein product [Mus musculus]
HG1000061N0_5000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000065N0_5000_gene_prediction1	gi 5031571 ref NP_005713.1  actin-related protein 2; ARP2 (actin-related protein 2, yeast) homolog [Homo sapiens]
HG1000065N0_10000_gene_prediction1	gi 13386220 ref NP_081610.1  RIKEN cDNA 2210414H16 [Mus musculus]
HG1000065N0_160000_gene_prediction1	gi 13386220 ref NP_081610.1  RIKEN cDNA 2210414H16 [Mus musculus]
HG1000068N0_160000_gene_prediction1	gi 13386220 ref NP_081610.1  RIKEN cDNA 2210414H16 [Mus musculus]
HG1000070N0_0_gene_prediction1	gi 26326191 dbj BAC26839.1  unnamed protein product [Mus musculus]
HG1000073N0_20000_gene_prediction1	gi 21595527 gb AAH32275.1  Similar to receptor-like tyrosine kinase [Mus musculus]
HG1000075N0_160000_gene_prediction1	gi 26326407 dbj BAC26947.1  unnamed protein product [Mus musculus]
HG1000076N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000081N0_160000_gene_prediction1	gi 4502549 ref NP_001734.1  calmodulin 2 (phosphorylase kinase, delta); phosphorylase kinase delta [Homo sapiens]
HG1000106N0_160000_gene_prediction1	gi 6680305 ref NP_032328.1  heat shock protein, 84 kDa 1 [Mus musculus]
HG1000107N0_160000_gene_prediction1	gi 6681225 ref NP_031905.1  developmentally regulated GTP binding protein 1; developmentally regulated GTP-binding protein 1 [Mus musculus]
HG1000109N0_0_gene_prediction1	gi 6754774 ref NP_034986.1  myosin heavy chain, cardiac muscle, adult; alpha cardiac MHC; alpha myosin [Mus musculus]
HG1000112N0_160000_gene_prediction1	gi 23956080 ref NP_058675.1  putative serine/threonine kinase [Mus musculus]
HG1000116N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000126N0_160000_gene_prediction1	gi 6680305 ref NP_032328.1  heat shock protein, 84 kDa 1 [Mus musculus]
HG1000130N0_160000_gene_prediction1	gi 20825377 ref XP_143696.1  similar to hypothetical protein dJ12208.2 [Homo sapiens] [Mus musculus]
HG1000132N0_160000_gene_prediction1	gi 6754208 ref NP_034569.1  high mobility group box 1; high mobility group protein 1

FP ID	Fantom Top Hit Annotation
	[Mus musculus]
HG1000133N0_160000_gene_prediction1	gi 26347765 dbj BAC37531.1  unnamed protein product [Mus musculus]
HG1000134N0_20000_gene_prediction1	gi 26382599 dbj BAB22733.2  unnamed protein product [Mus musculus]
HG1000134N0_20000_gene_prediction2	gi 26353738 dbj BAC40499.1  unnamed protein product [Mus musculus]
HG1000142N0_160000_gene_prediction1	gi 26353738 dbj BAC40499.1  unnamed protein product [Mus musculus]
HG1000144N0_20000_gene_prediction1	gi 6679108 ref NP_032748.1  nucleophosmin 1; nucleolar protein NO38 [Mus musculus]
HG1000145N0_160000_gene_prediction1	gi 6677779 ref NP_033107.1  ribosomal protein L28; DNA segment, Chr 7, Wayne State University 21, expressed [Mus musculus]
HG1000146N0_160000_gene_prediction1	gi 6677779 ref NP_033107.1  ribosomal protein L28; DNA segment, Chr 7, Wayne State University 21, expressed [Mus musculus]
HG1000150N0_10000_gene_prediction1	gi 3717978 emb CAA73041.1  5S ribosomal protein [Mus musculus]
HG1000152N0_160000_gene_prediction1	gi 11037798 ref NP_067621.1  dynactin 5; dynactin 4; p25 dynactin subunit [Mus musculus]
HG1000161N0_160000_gene_prediction1	gi 21536242 ref NP_573499.1  glucocorticoid induced transcript 1; testhymin; thymocyte/spermatocyte selection 1 [Mus musculus]
HG1000163N0_160000_gene_prediction1	gi 20819730 ref XP_129359.1  hypothetical protein XP_129359 [Mus musculus]
HG1000164N0_5000_gene_prediction1	gi 20835770 ref XP_132127.1  similar to 60S RIBOSOMAL PROTEIN L13 [Mus musculus]
HG1000165N0_1000_gene_prediction1	gi 26340448 dbj BAC33887.1  unnamed protein product [Mus musculus]
HG1000166N0_160000_gene_prediction2	gi 26353666 dbj BAC40463.1  unnamed protein product [Mus musculus]
HG1000167N0_160000_gene_prediction1	gi 27369878 ref NP_766203.1  hypothetical protein 5330403K09 [Mus musculus]
HG1000171N0_40000_gene_prediction1	gi 26354683 dbj BAC40968.1  unnamed protein product [Mus musculus]
HG1000171N0_160000_gene_prediction1	gi 26325838 dbj BAC26673.1  unnamed protein product [Mus musculus]
HG1000175N0_160000_gene_prediction2	gi 26325838 dbj BAC26673.1  unnamed protein product [Mus musculus]
HG1000176N0_1000_gene_prediction1	gi 26354216 dbj BAC40736.1  unnamed protein product [Mus musculus]

FP ID	Fantom Top Hit Annotation
HG1000176N0_160000_gene_prediction1	gi 26337635 dbj BAC32503.1  unnamed protein product [Mus musculus]
HG1000177N0_160000_gene_prediction1	gi 26337635 dbj BAC32503.1  unnamed protein product [Mus musculus]
HG1000178N0_160000_gene_prediction1	gi 20884040 ref XP_134731.1  endothelial differentiation, sphingolipid G-protein-coupled receptor, 5 [Mus musculus]
HG1000178N0_160000_gene_prediction2	gi 13384830 ref NP_079706.1  RIKEN cDNA 1110066C01 [Mus musculus]
HG1000180N0_1000_gene_prediction1	gi 13384830 ref NP_079706.1  RIKEN cDNA 1110066C01 [Mus musculus]
HG1000181N0_10000_gene_prediction1	gi 13384730 ref NP_079640.1  RIKEN cDNA 1110005A23 [Mus musculus]
HG1000181N0_160000_gene_prediction1	gi 25023031 ref XP_205093.1  similar to hypothetical protein FLJ38281 [Homo sapiens] [Mus musculus]
HG1000183N0_160000_gene_prediction1	gi 26334755 dbj BAC31078.1  unnamed protein product [Mus musculus]
HG1000186N0_20000_gene_prediction1	gi 27370150 ref NP_766364.1  hypothetical protein D630002G06 [Mus musculus]
HG1000186N0_160000_gene_prediction2	
HG1000187N0_20000_gene_prediction1	gi 26342222 dbj BAC34773.1  unnamed protein product [Mus musculus]
HG1000187N0_160000_gene_prediction3	
	gi 25024769 ref XP_207136.1  similar to ORF2 [Mus musculus domesticus]
HG1000189N0_1000_gene_prediction1	
HG1000189N0_5000_gene_prediction1	gi 26325734 dbj BAC26621.1  unnamed protein product [Mus musculus]
	gi 20879992 ref XP_140210.1  similar to BG:DS01759.1 gene product [Drosophila melanogaster] [Mus musculus]
HG1000189N0_1000_gene_prediction2	
HG1000189N0_5000_gene_prediction2	gi 26325734 dbj BAC26621.1  unnamed protein product [Mus musculus]
	gi 20879992 ref XP_140210.1  similar to BG:DS01759.1 gene product [Drosophila melanogaster] [Mus musculus]
HG1000195N0_10000_gene_prediction1	
HG1000199N0_160000_gene_prediction1	gi 17390530 gb AAH18231.1  Unknown (protein for MGC:19236) [Mus musculus]
HG1000201N0_10000_gene_prediction1	gi 20824845 ref XP_131963.1  expressed sequence C77020 [Mus musculus]
	gi 27477269 ref XP_209223.1  similar to Transforming protein RhoC (H9) [Homo

FP ID	Fantom Top Hit Annotation
	sapiens]
HG1000204N0_10000_gene_prediction1	gi 26333233 dbj BAC30334.1  unnamed protein product [Mus musculus]
HG1000209N0_160000_gene_prediction2	gi 26326739 dbj BAC27113.1  unnamed protein product [Mus musculus]
HG1000215N0_5000_gene_prediction1	gi 27369784 ref NP_766142.1  hypothetical protein A230053P19 [Mus musculus]
	gi 6671756 ref NP_031732.1  suppressor of cytokine signaling 2; cytokine inducible SH2-containing protein 2; high growth; STAT-induced STAT inhibitor 2; cytokine-inducible SH2 protein 2 [Mus musculus]
HG1000215N0_1000_gene_prediction1	
HG1000219N0_10000_gene_prediction1	gi 26328915 dbj BAC28196.1  unnamed protein product [Mus musculus]
	gi 4504255 ref NP_002097.1  H2A histone family, member Z; H2AZ histone [Homo sapiens]
HG1000221N0_160000_gene_prediction1	
HG1000221N0_20000_gene_prediction1	gi 11360345 pir T42725 actin binding protein ACF7, neural isoform 1 - mouse (fragment)
HG1000223N0_160000_gene_prediction1	gi 11360345 pir T42725 actin binding protein ACF7, neural isoform 1 - mouse (fragment)
	gi 25019988 ref XP_207469.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
HG1000225N0_160000_gene_prediction1	
	gi 20137004 ref NP_035320.1  proteasome (prosome, macropain) 28 subunit, beta; protease (prosome, macropain) 28 subunit, beta [Mus musculus]
HG1000235N0_160000_gene_prediction1	
	gi 15617197 ref NP_077135.1  ATPase, H+ transporting, lysosomal 13kD, V1 subunit G isoform 1; ATPase, H+ transporting, lysosomal (vacuolar proton pump) [Mus musculus]
HG1000236N0_160000_gene_prediction1	
HG1000238N0_160000_gene_prediction1	gi 6671704 ref NP_031664.1  chaperonin subunit 7 (eta) [Mus musculus]
	gi 6671549 ref NP_031479.1  anti-oxidant protein 2; acidic calcium-independent phospholipase A2; peroxiredoxin 5; 1-Cys Prx [Mus musculus]
HG1000238N0_5000_gene_prediction1	
	gi 6671549 ref NP_031479.1  anti-oxidant protein 2; acidic calcium-independent phospholipase A2; peroxiredoxin 5; 1-Cys Prx [Mus musculus]
HG1000239N0_160000_gene_prediction1	
HG1000241N0_160000_gene_prediction1	gi 7657357 ref NP_056596.1  nucleosome assembly protein 1-like 1; nucleosome assembly protein-1 [Mus musculus]



FP ID	Fantom Top Hit Annotation
HG1000243N0_160000_gene_prediction1	gi 4759158 ref NP_004588.1  small nuclear ribonucleoprotein D2 polypeptide 16.5kDa; small nuclear ribonucleoprotein D2 polypeptide (16.5kD) [Homo sapiens]
HG1000243N0_160000_gene_prediction2	gi 8393534 ref NP_058653.1  high mobility group protein 17 [Mus musculus]
HG1000245N0_1000_gene_prediction1	gi 8393534 ref NP_058653.1  high mobility group protein 17 [Mus musculus]
HG1000250N0_160000_gene_prediction1	gi 12850132 dbj BAB28604.1  unnamed protein product [Mus musculus]
HG1000252N0_160000_gene_prediction1	gi 20824845 ref XP_131963.1  expressed sequence C77020 [Mus musculus]
HG1000255N0_10000_gene_prediction1	gi 17105394 ref NP_000975.2  ribosomal protein L23a; 60S ribosomal protein L23a; melanoma differentiation-associated gene 20 [Homo sapiens]
HG1000262N0_160000_gene_prediction2	gi 13385532 ref NP_080303.1  RIKEN cDNA 2700086I23 [Mus musculus]
HG1000263N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000264N0_5000_gene_prediction1	gi 26360198 dbj BAB25612.2  unnamed protein product [Mus musculus]
HG1000264N0_5000_gene_prediction2	gi 21624617 ref NP_081018.1  RIKEN cDNA 1110007M04 [Mus musculus]
HG1000265N0_160000_gene_prediction1	gi 21624617 ref NP_081018.1  RIKEN cDNA 1110007M04 [Mus musculus]
HG1000266N0_0_gene_prediction1	gi 25070241 ref XP_192786.1  proline rich protein expressed in brain [Mus musculus]
HG1000266N0_160000_gene_prediction1	gi 12584972 ref NP_075021.1  lipin 3 [Mus musculus]
HG1000267N0_5000_gene_prediction1	gi 26340094 dbj BAC33710.1  unnamed protein product [Mus musculus]
HG1000270N0_160000_gene_prediction1	gi 6679937 ref NP_032110.1  glyceraldehyde-3-phosphate dehydrogenase [Mus musculus]
HG1000271N0_10000_gene_prediction1	gi 12844196 dbj BAB26273.1  unnamed protein product [Mus musculus]
HG1000271N0_160000_gene_prediction1	gi 26345908 dbj BAC36605.1  unnamed protein product [Mus musculus]
HG1000273N0_160000_gene_prediction1	gi 26345908 dbj BAC36605.1  unnamed protein product [Mus musculus]
HG1000295N0_160000_gene_prediction1	gi 20888943 ref XP_129258.1  cDNA sequence AF233884 [Mus musculus]
HG1000296N0_160000_gene_prediction1	gi 21313266 ref NP_080089.1  RIKEN cDNA 1200003O06 [Mus musculus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000299N0_160000_gene_prediction1	gi 25054735 ref XP_192839.1  ATPase, class II, type 9B [Mus musculus]
HG1000300N0_10000_gene_prediction1	gi 6753882 ref NP_034349.1  FK506 binding protein 4 (59 kDa) [Mus musculus]
HG1000306N0_0_gene_prediction1	gi 25024769 ref XP_207136.1  similar to ORF2 [Mus musculus domesticus]
HG1000306N0_0_gene_prediction2	
HG1000312N0_160000_gene_prediction1	
HG1000314N0_1000_gene_prediction1	gi 4506283 ref NP_003454.1  protein tyrosine phosphatase type IVA, member 1; Protein tyrosine phosphatase IVA1 [Homo sapiens]
HG1000315N0_160000_gene_prediction1	gi 4506285 ref NP_003470.1  protein tyrosine phosphatase type IVA, member 2, isoform 1; protein tyrosine phosphatase IVA; protein tyrosine phosphatase IVA2; phosphatase of regenerating liver 2 [Homo sapiens]
HG1000330N0_160000_gene_prediction2	gi 6679553 ref NP_033003.1  protein tyrosine phosphatase, non-receptor type 2 [Mus musculus]
HG1000330N0_160000_gene_prediction4	gi 12860388 dbj BAB31939.1  unnamed protein product [Mus musculus]
HG1000332N0_10000_gene_prediction1	gi 26344091 dbj BAC35702.1  unnamed protein product [Mus musculus]
HG1000337N0_1000_gene_prediction1	gi 20987322 gb AAH30185.1  Unknown (protein for MGC:29401) [Mus musculus]
HG1000341N0_5000_gene_prediction1	gi 4506725 ref NP_000998.1  ribosomal protein S4, X-linked X isoform; 40S ribosomal protein S4, X isoform; ribosomal protein S4X isoform; single-copy abundant mRNA; cell cycle gene 2 [Homo sapiens]
HG1000341N0_10000_gene_prediction1	gi 26332837 dbj BAC30136.1  unnamed protein product [Mus musculus]
HG1000353N0_160000_gene_prediction1	gi 17157989 ref NP_473384.1  Musashi homolog 2 (Drosophila) [Mus musculus]
HG1000357N0_20000_gene_prediction1	gi 25021483 ref XP_207941.1  similar to Retrovirus-related POL polypeptide [Mus musculus]
HG1000358N0_5000_gene_prediction1	gi 27372319 dbj BAC53724.1  Piccolo [Mus musculus]
HG1000359N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000363N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000364N0_160000_gene_prediction1	gi 19484126 gb AAH25846.1  Unknown (protein for MGC:32383) [Mus musculus]
HG1000367N0_160000_gene_prediction1	gi 13928676 ref NP_113687.1  proline rich protein 2 [Mus musculus]
HG1000379N0_160000_gene_prediction1	gi 20863632 ref XP_164160.1  hypothetical protein XP_164160 [Mus musculus]
HG1000390N0_10000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000390N0_5000_gene_prediction1	gi 20892585 ref XP_147977.1  RIKEN cDNA 2610001E17 [Mus musculus]
HG1000391N0_160000_gene_prediction1	gi 20892585 ref XP_147977.1  RIKEN cDNA 2610001E17 [Mus musculus]
HG1000396N0_160000_gene_prediction2	gi 26330368 dbj BAC28914.1  unnamed protein product [Mus musculus]
HG1000401N0_10000_gene_prediction1	
HG1000407N0_160000_gene_prediction1	gi 12853695 dbj BAB29819.1  unnamed protein product [Mus musculus]
HG1000408N0_160000_gene_prediction2	gi 25029560 ref XP_203691.1  similar to PROBABLE POL POLYPROTEIN [Mus musculus]
HG1000414N0_160000_gene_prediction2	gi 26326871 dbj BAC27179.1  unnamed protein product [Mus musculus]
HG1000416N0_160000_gene_prediction1	gi 20902061 ref XP_147959.1  hypothetical protein XP_147959 [Mus musculus]
HG1000428N0_160000_gene_prediction1	gi 25032567 ref XP_207391.1  similar to ORF2 [Mus musculus domesticus]
HG1000429N0_160000_gene_prediction1	gi 25022040 ref XP_204233.1  similar to ORF2 [Mus musculus domesticus]
HG1000431N0_20000_gene_prediction1	gi 26339864 dbj BAC33595.1  unnamed protein product [Mus musculus]
HG1000435N0_160000_gene_prediction1	gi 8394057 ref NP_058565.1  low density lipoprotein receptor-related protein 4; low density lipoprotein-related protein 4; Low Density Lipoprotein Receptor Related Protein 4; corin [Mus musculus]
HG1000441N0_160000_gene_prediction1	gi 26340972 dbj BAC34148.1  unnamed protein product [Mus musculus]
HG1000441N0_160000_gene_prediction2	gi 12836479 dbj BAB23675.1  unnamed protein product [Mus musculus]
HG1000446N0_160000_gene_prediction1	gi 25029827 ref XP_207226.1  similar to ORF2 [Mus musculus domesticus]
HG1000446N0_160000_gene_prediction2	gi 25031497 ref XP_207552.1  similar to Retrovirus-related POL polyprotein [Mus

FP ID	Fantom Top Hit Annotation
	musculus]
HG1000449N0_160000_gene_prediction2	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000451N0_160000_gene_prediction1	gi 25054021 ref XP_192811.1  similar to Transmembrane protease, serine 2 (Epitheliasin) (Plasmic transmembrane protein X) [Mus musculus]
HG1000455N0_10000_gene_prediction1	gi 20846744 ref XP_144090.1  similar to hypothetical protein FLJ12457 [Mus musculus]
HG1000461N0_10000_gene_prediction1	gi 20824899 ref XP_144255.1  hypothetical protein XP_144255 [Mus musculus]
	gi 12853695 dbj BAB29819.1  unnamed protein product [Mus musculus]
HG1000474N0_5000_gene_prediction1	gi 12834707 dbj BAB23011.1  unnamed protein product [Mus musculus]
HG1000476N0_1000_gene_prediction1	
HG1000489N0_160000_gene_prediction1	no blast hit
HG1000499N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000500N0_160000_gene_prediction1	gi 20912903 ref XP_126663.1  RIKEN cDNA 2410154J16 [Mus musculus]
HG1000505N0_160000_gene_prediction1	gi 25044951 ref XP_195302.1  similar to olfactory receptor MOR256-23 [Mus musculus]
HG1000509N0_10000_gene_prediction1	gi 26334721 dbj BAC31061.1  unnamed protein product [Mus musculus]
HG1000510N0_160000_gene_prediction1	gi 12834707 dbj BAB23011.1  unnamed protein product [Mus musculus]
HG1000513N0_160000_gene_prediction1	gi 12859663 dbj BAB31727.1  unnamed protein product [Mus musculus]
	gi 119146 sp P20001 EF11_CRIGR Elongation factor 1-alpha 1 (EF-1-alpha-1) (Elongation factor 1 A-1) (eEF1A-1) (Elongation factor Tu) (EF-Tu)
HG1000519N0_160000_gene_prediction1	
HG1000521N0_160000_gene_prediction1	gi 2495301 sp Q63934 BR3B_MOUSE Brain-specific homeobox/POU domain protein 3B (BRN-3B) (BRN-3.2)
HG1000524N0_160000_gene_prediction1	gi 21280325 dbj BAB96760.1  type XXVI collagen [Mus musculus]
	gi 6679921 ref NP_032102.1  gamma-aminobutyric acid (GABA-A) receptor, subunit rho 2 [Mus musculus]
HG1000530N0_20000_gene_prediction1	
HG1000530N0_160000_gene_prediction2	gi 23622684 ref XP_156394.2  expressed sequence AL023001 [Mus musculus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000534N0_160000_gene_prediction1	
HG1000545N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000549N0_160000_gene_prediction1	gi 26341288 dbj BAC34306.1  unnamed protein product [Mus musculus]
HG1000549N0_160000_gene_prediction2	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000549N0_160000_gene_prediction3	gi 21312126 ref NP_081135.1  RIKEN cDNA 1110068E11 [Mus musculus]
HG1000553N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000560N0_160000_gene_prediction2	gi 25032555 ref XP_207412.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
HG1000562N0_160000_gene_prediction1	
HG1000566N0_40000_gene_prediction1	gi 20856064 ref XP_151615.1  hypothetical protein XP_151615 [Mus musculus]
HG1000566N0_160000_gene_prediction1	
HG1000582N0_160000_gene_prediction1	gi 7656873 ref NP_056579.1  RIKEN cDNA 5730583K22 gene [Mus musculus]
HG1000598N0_160000_gene_prediction1	gi 4512261 dbj BAA75227.1  neurochondrin-2 [Mus musculus]
HG1000606N0_20000_gene_prediction1	gi 19527094 ref NP_598640.1  expressed sequence AI327031 [Mus musculus]
HG1000607N0_160000_gene_prediction1	gi 25058382 ref XP_206318.1  hypothetical protein XP_206318 [Mus musculus]
HG1000608N0_20000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000616N0_1000_gene_prediction1	gi 26387941 dbj BAC25633.1  unnamed protein product [Mus musculus]
HG1000622N0_160000_gene_prediction2	
HG1000623N0_160000_gene_prediction1	gi 20904129 ref XP_155605.1  hypothetical protein XP_155605 [Mus musculus]
HG1000624N0_160000_gene_prediction1	gi 13542693 gb AAH05553.1  putative chloride channel (similar to Mm Clcn4-2) [Mus musculus]
HG1000625N0_160000_gene_prediction1	gi 20901495 ref XP_140099.1  RIKEN cDNA 9130404H23 [Mus musculus]
HG1000628N0_40000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]

FP ID	Fantom Top Hit Annotation
HG1000628N0_20000_gene_prediction 1	gi 26339720 dbj BAC33523.1  unnamed protein product [Mus musculus]
HG1000638N0_5000_gene_prediction 1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000642N0_160000_gene_predictio n1	
HG1000646N0_160000_gene_predictio n1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000649N0_160000_gene_predictio n1	gi 25049717 ref XP_149640.2  similar to gene Dbp73D protein - fruit fly (Drosophila melanogaster) [Mus musculus]
HG1000650N0_160000_gene_predictio n1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000652N0_160000_gene_predictio n2	gi 26377673 dbj BAC25377.1  unnamed protein product [Mus musculus]
HG1000656N0_160000_gene_predictio n1	gi 13384666 ref NP_079583.1  nuclear receptor binding factor 2 [Mus musculus]
HG1000656N0_160000_gene_predictio n2	gi 25050704 ref XP_133465.2  RIKEN cDNA 2410004H02 [Mus musculus]
HG1000659N0_20000_gene_prediction 1	gi 25050704 ref XP_133465.2  RIKEN cDNA 2410004H02 [Mus musculus]
HG1000661N0_20000_gene_prediction 1	gi 26333733 dbj BAC30584.1  unnamed protein product [Mus musculus]
HG1000664N0_160000_gene_predictio n1	gi 27372319 dbj BAC53724.1  Piccolo [Mus musculus]
HG1000670N0_160000_gene_predictio n1	gi 6680195 ref NP_032255.1  histone deacetylase 2; DNA segment, Chr 10, Wayne State University 179, expressed [Mus musculus]
HG1000685N0_160000_gene_predictio n2	gi 17313266 ref NP_478121.1  RecQ protein- like 4 [Mus musculus]
HG1000690N0_20000_gene_prediction 1	
HG1000690N0_20000_gene_prediction 2	gi 26340662 dbj BAC33993.1  unnamed protein product [Mus musculus]
HG1000696N0_20000_gene_prediction 1	gi 26340662 dbj BAC33993.1  unnamed protein product [Mus musculus]
HG1000696N0_40000_gene_prediction 1	gi 26326171 dbj BAC26829.1  unnamed protein product [Mus musculus]
HG1000697N0_160000_gene_predictio n1	gi 25024387 ref XP_207341.1  hypothetical protein XP_207341 [Mus musculus]
HG1000700N0_160000_gene_predictio n2	gi 26351279 dbj BAC39276.1  unnamed protein product [Mus musculus]
HG1000704N0_160000_gene_predictio n1	gi 21644579 ref NP_660253.1  Williams-

FP ID	Fantom Top Hit Annotation
n1	Beuren syndrome critical region gene 17 [Mus musculus]
HG1000711N0_20000_gene_prediction 1	gi 23273683 gb AAH37239.1  Similar to BCL2-associated athanogene 4 [Mus musculus]
HG1000738N0_160000_gene_prediction n1	gi 12856848 dbj BAB30802.1  unnamed protein product [Mus musculus]
HG1000739N0_160000_gene_prediction n1	gi 26339470 dbj BAC33406.1  unnamed protein product [Mus musculus]
HG1000739N0_160000_gene_prediction n2	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000740N0_10000_gene_prediction 1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000743N0_160000_gene_prediction n1	gi 23601536 ref XP_130965.2  Nice-4 protein homolog [Mus musculus]
HG1000779N0_160000_gene_prediction n1	gi 2627027 dbj BAA23475.1  Ftp-1 [Mus musculus]
HG1000781N0_160000_gene_prediction n1	gi 25023334 ref XP_204722.1  similar to formin [Mus musculus]
HG1000781N0_160000_gene_prediction n2	gi 26350877 dbj BAC39075.1  unnamed protein product [Mus musculus]
HG1000786N0_160000_gene_prediction n1	gi 25023581 ref XP_207103.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
HG1000788N0_1000_gene_prediction n1	gi 26340832 dbj BAC34078.1  unnamed protein product [Mus musculus]
HG1000799N0_20000_gene_prediction 1	gi 20847912 ref XP_144610.1  similar to KIAA1904 protein [Homo sapiens] [Mus musculus]
HG1000808N0_160000_gene_prediction n1	gi 26345960 dbj BAC36631.1  unnamed protein product [Mus musculus]
HG1000817N0_160000_gene_prediction n1	gi 20882231 ref XP_139203.1  similar to KIAA0858 protein [Homo sapiens] [Mus musculus]
HG1000822N0_20000_gene_prediction 1	gi 13242237 ref NP_077327.1  Heat shock cognate protein 70; heat shock 70kD protein 8 [Rattus norvegicus]
HG1000824N0_160000_gene_prediction n1	gi 6680195 ref NP_032255.1  histone deacetylase 2; DNA segment, Chr 10, Wayne State University 179, expressed [Mus musculus]
HG1000824N0_10000_gene_prediction 1	gi 20883564 ref XP_152815.1  hypothetical protein XP_152815 [Mus musculus]
HG1000839N0_160000_gene_prediction n1	gi 20883564 ref XP_152815.1  hypothetical protein XP_152815 [Mus musculus]

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
HG1000842N0_160000_gene_prediction1	gi 26339496 dbj BAC33419.1  unnamed protein product [Mus musculus]
HG1000842N0_160000_gene_prediction2	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000869N0_160000_gene_prediction1	gi 6715564 ref NP_032607.1  melanoma antigen, 80 kDa [Mus musculus]
HG1000870N0_160000_gene_prediction1	gi 20881174 ref XP_147875.1  hypothetical protein XP_147875 [Mus musculus]
HG1000870N0_160000_gene_prediction2	gi 27369942 ref NP_766246.1  hypothetical protein 9530051F04 [Mus musculus]
HG1000878N0_20000_gene_prediction1	gi 27369942 ref NP_766246.1  hypothetical protein 9530051F04 [Mus musculus]
HG1000878N0_20000_gene_prediction2	gi 27369942 ref NP_766246.1  hypothetical protein 9530051F04 [Mus musculus]
HG1000904N0_160000_gene_prediction2	gi 27369942 ref NP_766246.1  hypothetical protein 9530051F04 [Mus musculus]
HG1000904N0_40000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000906N0_5000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000906N0_160000_gene_prediction2	gi 20836822 ref XP_130277.1  similar to Plakophilin 4 (p0071) [Mus musculus]
HG1000910N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000948N0_160000_gene_prediction1	gi 26325846 dbj BAC26677.1  unnamed protein product [Mus musculus]
HG1000955N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1000959N0_160000_gene_prediction1	gi 7670427 dbj BAA95065.1  unnamed protein product [Mus musculus]
HG1000959N0_5000_gene_prediction1	gi 22507385 ref NP_081019.1  RIKEN cDNA 1110014F12 [Mus musculus]
HG1000990N0_5000_gene_prediction1	gi 22507385 ref NP_081019.1  RIKEN cDNA 1110014F12 [Mus musculus]
HG1000994N0_10000_gene_prediction1	gi 10946762 ref NP_067382.1  triggering receptor expressed on myeloid cells 3; triggering receptor expressed on monocytes 3 [Mus musculus]
HG1000994N0_160000_gene_prediction2	gi 12855175 dbj BAB30238.1  unnamed protein product [Mus musculus]
HG1000994N0_10000_gene_prediction2	gi 12855175 dbj BAB30238.1  unnamed protein product [Mus musculus]
HG1001001N0_160000_gene_prediction1	gi 12855175 dbj BAB30238.1  unnamed protein product [Mus musculus]



FP ID	Fantom Top Hit Annotation
HG1001001N0_0_gene_prediction1	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1001002N0_160000_gene_prediction1	gi 27370034 ref NP_766297.1  hypothetical protein A530025J20 [Mus musculus]
HG1001003N0_0_gene_prediction1	gi 20348159 ref XP_111588.1  similar to TRAV9D-3 [Mus musculus]
HG1001007N0_160000_gene_prediction2	gi 27370034 ref NP_766297.1  hypothetical protein A530025J20 [Mus musculus]
HG1001011N0_160000_gene_prediction1	gi 13097000 gb AAH03291.1  Similar to hypothetical protein FLJ10342 [Mus musculus]
HG1001011N0_160000_gene_prediction2	gi 26336525 dbj BAC31945.1  unnamed protein product [Mus musculus]
HG1001014N0_160000_gene_prediction1	gi 25047957 ref XP_130582.2  similar to hypothetical protein MGC14161 [Homo sapiens] [Mus musculus]
HG1001014N0_5000_gene_prediction1	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1001017N0_160000_gene_prediction1	gi 26337385 dbj BAC32378.1  unnamed protein product [Mus musculus]
HG1001020N0_160000_gene_prediction1	gi 25019831 ref XP_207463.1  similar to CD59B [Mus musculus]
HG1001024N0_160000_gene_prediction1	gi 26338976 dbj BAC33159.1  unnamed protein product [Mus musculus]
HG1001024N0_160000_gene_prediction2	gi 20915148 ref XP_149841.1  hypothetical protein XP_149841 [Mus musculus]
HG1001031N0_160000_gene_prediction1	gi 20915148 ref XP_149841.1  hypothetical protein XP_149841 [Mus musculus]
HG1001035N0_5000_gene_prediction1	gi 25071690 ref XP_193591.1  hypothetical protein XP_193591 [Mus musculus]
HG1001043N0_160000_gene_prediction1	gi 26347249 dbj BAC37273.1  unnamed protein product [Mus musculus]
HG1001046N0_5000_gene_prediction1	gi 6678714 ref NP_032537.1  lymphoid-restricted membrane protein [Mus musculus]
HG1001046N0_160000_gene_prediction1	gi 25048969 ref XP_143803.3  similar to bA4O1.1 (novel protein) [Homo sapiens] [Mus musculus]
HG1001047N0_1000_gene_prediction1	gi 25021180 ref XP_207917.1  similar to RNP particle component [Mus musculus]
HG1001048N0_160000_gene_prediction1	gi 26353724 dbj BAC40492.1  unnamed protein product [Mus musculus]
HG1001048N0_160000_gene_prediction2	gi 20343845 ref XP_109652.1  similar to hypothetical protein FLJ25217 [Homo sapiens] [Mus musculus]
HG1001144N0_20000_gene_prediction	gi 20346197 ref XP_110161.1  RAN binding

FP ID	Fantom Top Hit Annotation
1	protein 1 [Mus musculus]
HG1001148N0_160000_gene_prediction2	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001172N0_160000_gene_prediction1	gi 26339628 dbj BAC33485.1  unnamed protein product [Mus musculus]
HG1001172N0_20000_gene_prediction1	gi 22122489 ref NP_666128.1  hypothetical protein MGC38936 [Mus musculus]
HG1001187N0_160000_gene_prediction1	gi 26340706 dbj BAC34015.1  unnamed protein product [Mus musculus]
HG1001192N0_160000_gene_prediction1	gi 18497290 ref NP_084056.1  protein kinase raf 1; murine sarcoma 3611 oncogene 1; sarcoma 3611 oncogene [Mus musculus]
HG1001194N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001199N0_160000_gene_prediction1	gi 20837732 ref XP_132241.1  hypothetical protein XP_132241 [Mus musculus]
HG1001199N0_160000_gene_prediction2	gi 20071068 gb AAH27341.1  Similar to elongation factor G2 [Mus musculus]
HG1001220N0_160000_gene_prediction1	gi 20071068 gb AAH27341.1  Similar to elongation factor G2 [Mus musculus]
HG1001223N0_160000_gene_prediction1	gi 20908735 ref XP_122598.1  similar to helix-destabilizing protein - rat [Mus musculus]
HG1001229N0_160000_gene_prediction2	gi 25024769 ref XP_207136.1  similar to ORF2 [Mus musculus domesticus]
HG1001230N0_5000_gene_prediction1	gi 6754206 ref NP_034568.1  hexokinase 1; downeast anemia [Mus musculus]
HG1001235N0_160000_gene_prediction1	gi 12857205 dbj BAB30930.1  unnamed protein product [Mus musculus]
HG1001235N0_10000_gene_prediction1	gi 21703918 ref NP_663438.1  hypothetical protein BC024118 [Mus musculus]
HG1001235N0_20000_gene_prediction1	gi 26339338 dbj BAC33340.1  unnamed protein product [Mus musculus]
HG1001235N0_160000_gene_prediction2	gi 26339338 dbj BAC33340.1  unnamed protein product [Mus musculus]
HG1001235N0_160000_gene_prediction3	gi 26340904 dbj BAC34114.1  unnamed protein product [Mus musculus]
HG1001260N0_160000_gene_prediction1	gi 26327795 dbj BAC27638.1  unnamed protein product [Mus musculus]
HG1001260N0_40000_gene_prediction1	gi 8922328 ref NP_060517.1  hypothetical protein FLJ10290 [Homo sapiens]
HG1001264N0_160000_gene_prediction1	gi 8922328 ref NP_060517.1  hypothetical protein FLJ10290 [Homo sapiens]
HG1001274N0_160000_gene_prediction1	gi 26383198 dbj BAC25520.1  unnamed protein

WO 2005/005597

PCT/US2003/027106

FP ID	Fantom Top Hit Annotation
n1	product [Mus musculus]
HG1001284N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001284N0_160000_gene_prediction2	gi 26326843 dbj BAC27165.1  unnamed protein product [Mus musculus]
HG1001292N0_160000_gene_prediction1	gi 26326843 dbj BAC27165.1  unnamed protein product [Mus musculus]
HG1001302N0_160000_gene_prediction1	gi 13097342 gb AAH03421.1  Similar to ATPase, H+ transporting, lysosomal (vacuolar proton pump) 31kD [Mus musculus]
HG1001313N0_160000_gene_prediction1	gi 12852631 dbj BAB29486.1  unnamed protein product [Mus musculus]
HG1001323N0_160000_gene_prediction1	gi 25053141 ref XP_193739.1  similar to betaine-homocysteine methyltransferase [Rattus norvegicus] [Mus musculus]
HG1001328N0_5000_gene_prediction1	gi 26347687 dbj BAC37492.1  unnamed protein product [Mus musculus]
HG1001328N0_40000_gene_prediction1	gi 26352918 dbj BAC40089.1  unnamed protein product [Mus musculus]
HG1001331N0_0_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001335N0_160000_gene_prediction1	gi 20381292 gb AAH27770.1  stromal cell derived factor receptor 2 [Mus musculus]
HG1001335N0_160000_gene_prediction2	gi 2193870 dbj BAA20419.1  reverse transcriptase [Mus musculus]
HG1001348N0_160000_gene_prediction1	gi 2193870 dbj BAA20419.1  reverse transcriptase [Mus musculus]
HG1001349N0_160000_gene_prediction1	gi 20846538 ref XP_150033.1  hypothetical protein XP_150033 [Mus musculus]
HG1001354N0_160000_gene_prediction1	gi 7305215 ref NP_038599.1  kinase suppressor of ras [Mus musculus]
HG1001361N0_160000_gene_prediction1	gi 6678690 ref NP_032525.1  LIM homeobox protein 5; LIM homeo box protein 5 [Mus musculus]
HG1001376N0_160000_gene_prediction1	gi 20345901 ref XP_109824.1  hypothetical protein XP_109824 [Mus musculus]
HG1001376N0_5000_gene_prediction1	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1001376N0_20000_gene_prediction1	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1001376N0_5000_gene_prediction2	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1001376N0_5000_gene_prediction3	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]

FP ID	Fantom Top Hit Annotation
HG1001417N0_160000_gene_prediction1	gi 27261816 ref NP_080861.1  RIKEN cDNA C530005J20 [Mus musculus]
HG1001417N0_1000_gene_prediction1	gi 26349767 dbj BAC38523.1  unnamed protein product [Mus musculus]
HG1001417N0_160000_gene_prediction2	gi 26349767 dbj BAC38523.1  unnamed protein product [Mus musculus]
HG1001417N0_160000_gene_prediction3	gi 26349767 dbj BAC38523.1  unnamed protein product [Mus musculus]
HG1001436N0_5000_gene_prediction1	gi 26349767 dbj BAC38523.1  unnamed protein product [Mus musculus]
HG1001436N0_20000_gene_prediction1	gi 20987280 gb AAH29643.1  Unknown (protein for MGC:25768) [Mus musculus]
HG1001436N0_160000_gene_prediction1	gi 25051637 ref XP_194491.1  RIKEN cDNA 1110053F02 [Mus musculus]
HG1001439N0_160000_gene_prediction1	gi 25051637 ref XP_194491.1  RIKEN cDNA 1110053F02 [Mus musculus]
HG1001484N0_160000_gene_prediction1	gi 6753290 ref NP_033943.1  calsequestrin 1 [Mus musculus]
HG1001485N0_10000_gene_prediction1	gi 25029827 ref XP_207226.1  similar to ORF2 [Mus musculus domesticus]
HG1001500N0_160000_gene_prediction1	gi 3599320 gb AAC72793.1  ORF2 [Mus musculus domesticus]
HG1001500N0_160000_gene_prediction2	gi 6679108 ref NP_032748.1  nucleophosmin 1; nucleolar protein NO38 [Mus musculus]
HG1001508N0_160000_gene_prediction1	gi 25029928 ref XP_207257.1  similar to Retrovirus-related POL polyprotein [Mus musculus]
	gi 20340683 ref XP_110361.1  similar to phospholipase C beta 2 [Rattus norvegicus] [Mus musculus]

### Examples

[0602] The examples, which are intended to be purely exemplary of the invention and should therefore not be considered to limit the invention in any way, also describe and detail aspects and embodiments of the invention discussed above. The examples are not intended to represent that the experiments below are all or the only experiments performed. Efforts have been made to ensure accuracy with respect to numbers used (e.g., amounts, temperature, etc.) but some experimental errors and deviations should be accounted for. Unless indicated otherwise, parts are parts by weight, molecular weight is weight average molecular weight, temperature is in degrees Centigrade, and pressure is at or near atmospheric.

[0603] While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications can be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective, spirit and scope of the present invention. All such modifications are intended to be within the scope of the claims appended hereto.

[0604] Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be realized and attained by means of the elements and combinations particularly pointed out in the appended claims. Moreover, advantages described in the body of the specification, if not included in the claims, are not per se limitations to the claimed invention.

[0605] It is to be understood that both the foregoing general description and the following detailed description are exemplary and explanatory only and are not restrictive of the invention, as claimed. Moreover, it must be understood that the invention is not limited to the particular embodiments described, as such may, of course, vary. Further, the terminology used to describe particular embodiments is not intended to be limiting, since the scope of the present invention will be limited only by its claims.

[0606] With respect to ranges of values, the invention encompasses each intervening value between the upper and lower limits of the range to at least a tenth of the lower limit's unit, unless the context clearly indicates otherwise. Further, the

invention encompasses any other stated intervening values. Moreover, the invention also encompasses ranges excluding either or both of the upper and lower limits of the range, unless specifically excluded from the stated range.

[0607] Unless defined otherwise, the meanings of all technical and scientific terms used herein are those commonly understood by one of ordinary skill in the art to which this invention belongs. One of ordinary skill in the art will also appreciate that any methods and materials similar or equivalent to those described herein can also be used to practice or test the invention. Further, all publications mentioned herein are incorporated by reference.

[0608] It must be noted that, as used herein and in the appended claims, the singular forms "a," "or," and "the" include plural referents unless the context clearly dictates otherwise. Thus, for example, reference to "a subject polypeptide" includes a plurality of such polypeptides and reference to "the agent" includes reference to one or more agents and equivalents thereof known to those skilled in the art, and so forth.

[0609] Further, all numbers expressing quantities of ingredients, reaction conditions, % purity, polypeptide and polynucleotide lengths, and so forth, used in the specification and claims, are modified by the term "about," unless otherwise indicated. Accordingly, the numerical parameters set forth in the specification and claims are approximations that may vary depending upon the desired properties of the present invention. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits, applying ordinary rounding techniques. Nonetheless, the numerical values set forth in the specific examples are reported as precisely as possible. Any numerical value, however, inherently contains certain errors from the standard deviation of its experimental measurement.

[0610] The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided may be different from the actual publication dates which may need to be independently confirmed.

### Example 1 Expression in *E. coli*

[0611] Sequences can be expressed in *E. coli*. Any one or more of the sequences according to SEQ ID NOS.: 1-104 can be expressed in *E. coli* by subcloning the entire coding region, or a selected portion thereof, into a prokaryotic expression vector. For example, the expression vector pQE16 from the QIA expression prokaryotic protein expression system (Qiagen, Valencia, CA) can be used. The features of this vector that make it useful for protein expression include an efficient promoter (phage T5) to drive transcription, expression control provided by the lac operator system, which can be induced by addition of IPTG (isopropyl-beta-D-thiogalactopyranoside), and an encoded 6XHis tag coding sequence. The latter is a stretch of six histidine amino acid residues which can bind very tightly to a nickel atom. This vector can be used to express a recombinant protein with a 6XHis tag fused to its carboxyl terminus, allowing rapid and efficient purification using Ni-coupled affinity columns.

[0612] The entire or the selected partial coding region can be amplified by PCR, then ligated into digested pQE16 vector. The ligation product can be transformed by electroporation into electrocompetent *E. coli* cells (for example, strain M15[pREP4] from Qiagen), and the transformed cells may be plated on ampicillin-containing plates. Colonies may then be screened for the correct insert in the proper orientation using a PCR reaction employing a gene-specific primer and a vector-specific primer. Also, positive clones can be sequenced to ensure correct orientation and sequence. To express the proteins, a colony containing a correct recombinant clone can be inoculated into L-Broth containing 100 µg/ml of ampicillin, and 25 µg/ml of kanamycin, and the culture allowed to grow overnight at 37 degrees C. The saturated culture may then be diluted 20-fold in the same medium and allowed to grow to an optical density of 0.5 at 600 nm. At this point, IPTG can be added to a final concentration of 1 mM to induce protein expression. After growing the culture for an additional 5 hours, the cells may be harvested by centrifugation at 3000 times g for 15 minutes.

[0613] The resultant pellet can be lysed with a mild, nonionic detergent in 20 mM Tris HCl (pH 7.5) (B PER.TM. Reagent from Pierce, Rockford, IL), or by sonication until the turbid cell suspension turns translucent. The resulting lysate can be further purified using a nickel-containing column (Ni-NTA spin column from

Qiagen) under non-denaturing conditions. Briefly, the lysate will be adjusted to 300 mM NaCl and 10 mM imidazole, then centrifuged at 700 times *g* through the nickel spin column to allow the His-tagged recombinant protein to bind to the column. The column will be washed twice with wash buffer (for example, 50 mM NaH<sub>2</sub> PO<sub>4</sub>, pH 8.0; 300 mM NaCl; 20 mM imidazole) and eluted with elution buffer (for example, 50 mM NaH<sub>2</sub> PO<sub>4</sub>, pH 8.0; 300 mM NaCl; 250 mM imidazole). All the above procedures will be performed at 4 degrees C. The presence of a purified protein of the predicted size can be confirmed with SDS-PAGE.

#### **Example 2: Expression in Mammalian Cells**

[0614] The sequences encoding the proteins of Example 1 can be cloned into the pENTR vector (Invitrogen) by PCR and transferred to the mammalian expression vector pDEST12.2 per manufacturer's instructions (Invitrogen). Introduction of the recombinant construct into the host cell can be effected by transfection with Eugene 6 (Roche) per manufacturer's instructions. The host cells containing one of polynucleotides of the invention can be used in conventional manners to produce the gene product encoded by the isolated fragment (in the case of an ORF). A number of types of cells can act as suitable host cells for expression of the proteins. Mammalian host cells include, for example, monkey COS cells, Chinese Hamster Ovary (CHO) cells, human kidney 293 cells, human epidermal A431 cells, human Colo205 cells, 3T3 cells, CV-1 cells, other transformed primate cell lines, normal diploid cells, cell strains derived from *in vitro* culture of primary tissue, primary explants, HeLa cells, mouse L cells, BHK, HL-60, U937, HaK or Jurkat cells.

#### **Example 3: Expression in Cell-Free Translation Systems**

[0615] Cell-free translation systems can also be employed to produce proteins using RNAs derived from the DNA constructs of the present invention. Appropriate cloning and expression vectors containing SP6 or T7 promoters for use with prokaryotic and eukaryotic hosts have been described (Sambrook et al., 1989). These DNA constructs can be used to produce proteins in a rabbit reticulocyte lysate system or in a wheat germ extract system.

[0616] Specific expression systems of interest include plant, bacterial, yeast, insect cell and mammalian cell derived expression systems. Expression systems in plants include those described in U.S. Patent No. 6,096,546 and U.S. Patent No. 6,127,145. Expression systems in bacteria include those described by Chang et al.,



1978, Goeddel et al., 1979, Goeddel et al., 1980, EP 0 036,776, U.S. Patent No. 4,551,433; DeBoer et al., 1983, and Siebenlist et al., 1980.

[0617] Mammalian expression is further accomplished as described in Dijkema et al. 1985, Gorman et al., 1982, Boshart et al., 1985, and U.S. Patent No. 4,399,216. Other features of mammalian expression are facilitated as described in Ham and Wallace, Meth. Enz., 1979, Barnes and Sato, 1980, U.S. Patent Nos. 4,767,704, 4,657,866, 4,927,762, 4,560,655, WO 90/103430, WO 87/00195, and U.S. RE 30,985.

#### **Example 4: Expression of the Secreted Factors in Yeast**

[0618] Primers can be designed to amplify the secreted factors using PCR and cloned into pENTR/D-TOPO vectors (Invitrogen, Carlsbad, CA). The secreted factors in pENTR/D-TOPO can be cloned into the yeast expression vector pYES-DEST52 by Gateway LR reaction (Invitrogen, Carlsbad, CA). The resulting yeast expression vectors can be transformed into INVSc1 strain from Invitrogen to express the secreted factors according to the manufacturer's protocol (Invitrogen, Carlsbad CA). The expressed secreted factors will have a 6XHis tag at the C-terminal. Expressed protein can be purified with ProBond™ resin (Invitrogen, Carlsbad, CA).

[0619] Expression systems in yeast include those described in Himmen et al., 1978, Ito et al., 1983, Kurtz et al., 1986, Kunze et al., 1985, Gleeson et al., 1986, Roggenkamp et al., 1986, Das et al., 1984, De Louvencourt et al., 1983, Van den Berg et al., 1990, Kunze et al., 1985, Cregg et al. 1985, U.S. Patent No. 4,837,148, U.S. Patent No. 4,929,555, Beach and Nurse, 1981, Davidow et al., 1985, Gaillardin et al., 1985, Ballance et al., 1983, Tilburn et al., 1983, Yelton et al., 1984, Kelly and Hynes, 1985, EP 0 244,234, and WO 91/00357.

#### **Example 5: Expression of Secreted Factors in Baculovirus Expression System.**

[0620] The secreted factors in pENTR/D-TOPO can be cloned into Baculovirus expression vector pDEST10 by Gateway LR reaction (Invitrogen, Carlsbad, CA). The secreted factors can be expressed by the Bac-to-Bac expression system from Invitrogen (Carlsbad CA), briefly described as follows. The expression vectors containing the secreted factors are transformed into competent DH10Bac™ *E. coli* strain and selected for transposition. The resulting *E. coli* contain recombinant bacmid that contains the secreted factor. High molecular weight DNA can be isolated from the *E. coli* containing the recombinant bacmid and then transfected into insect

cells with Cellfectin reagent. The expressed secreted factors will have a 6XHis tag at N-terminal. Expressed protein will be purified by ProBond™ resin (Invitrogen, Carlsbad, CA).

[0621] Expression of heterologous genes in insects can be accomplished as described in U.S. Patent No. 4,745,051; Doerfler *et al.*, 1987; Friesen *et al.*, 1986; EP 0 127,839, EP 0 155,476, Vlak *et al.*, 1988, Miller *et al.*, 1988, Carbonell *et al.*, 1988, Maeda *et al.*, 1985, Lebacq-Verheyden *et al.*, 1988, Smith *et al.*, 1985, Miyajima *et al.*; and Martin *et al.*, 1988. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts have been previously described (Setlow *et al.*, 1986, Luckow *et al.*, 1988; Miller *et al.*, 1986; Maeda *et al.*, 1985).

#### Example 6: Primer Design

[0622] To design the forward primer for PCR amplification, the melting point of the first 20 to 24 bases of the primer can be calculated by counting total A and T residues, then multiplying by 2. To design the reverse primer for PCR amplification, the melting point of the first 20 to 24 bases of the reverse complement, with the sequences written from 5-prime to 3-prime can be calculated by counting the total G and C residues, then multiplying by 4. Both start and stop codons can be present in the final amplified clone. The length of the primers is such to obtain melting temperatures within 63 degrees C to 68 degrees C. Adding the bases "CACC" to the forward primer renders it compatible for cloning the PCR product with the TOPO pENTR/D (Invitrogen, CA).

#### Example 7: Reverse Transcriptase Reaction

[0623] cDNA can be prepared by the following method. Between 200 ng and 1.0 µg mRNA is added to 2 µl DMSO and the volume adjusted to 11 µl with DEPC-treated water. One µl Oligo dT is added to the tube, and the mixture is heated at 70° C for 5 min., quickly chilled on ice for 2 min., and the mixture is collected at the bottom of the tube by brief centrifugation. The following 1<sup>st</sup> strand components are then added to the mRNA mixture: 2 µl 10X Stratascript (Stratagene, CA) 1<sup>st</sup> strand buffer, 1 µl 0.1 M DTT, 1 µl 10 mM dNTP mix (10 mM each of dG, dA, dT and dCTP), 1 µl RNase inhibitor, 3 µl Stratascript RT (50 U/ µl). The contents are gently mixed and the mixture collected by brief centrifugation. The mixture is incubated in a 42° C water bath for 1 hour, placed in a 70° C water bath for 15 min. to stop the reaction, transferred to ice for 2 min., and centrifuged briefly in a microfuge to collect the reaction product at the bottom of the reaction vessel. Two µl RNase H is then

added to the tube, the contents are mixed well, incubated at 37° C in a water bath for 20 min., and centrifuged briefly in a microfuge to collect the reaction product at the bottom of the reaction vessel. The reaction mixture can proceed directly to PCR or be stored at - 20° C.

#### **Example 8: Full Length PCR**

[0624] Full length PCR can be achieved by placing the products of the reaction described in Example 7, with primers diluted to 5µM in water, into a reaction vessel and adding a reaction mixture composed of 1x Taq buffer, 25 mM dNTP, 10 ng cDNA pool, TaqPlus (Stratagene, CA) (5u/ul), PfuTurbo (Stratagene, CA) (2.5u/ul), water. The contents of the reaction vessel are then mixed gently by inversion 5-6 times, placed into a reservoir where 2µl F<sub>1</sub>/R<sub>1</sub> primers are added, the plate sealed and placed in the thermocycler. The PCR reaction is comprised of the following eight steps. Step 1: 95° C for 3 min. Step 2: 94° C for 45 sec. Step 3: 0.5° C/sec to 56-60° C. Step 4: 56-60° C for 50 sec. Step 5: 72° C for 5 min. Step 6: Go to step 2, perform 35-40 cycles. Step 7: 72° C for 20 min. Step 8: 4° C.

[0625] The products can then be separated on a standard 0.8 to 1.0% agarose gel at 40 to 80 V, the bands of interest excised by cutting from the gel, and stored at - 20° C until extraction. The material in the bands of interest can be purified with QIAquick 96 PCR Purification Kit (Qiagen, CA) according to the manufacturer instructions. Cloning can be performed with the Topo Vector pENTR/D-TOPO vector (Invitrogen, CA) according to the manufacturer's instructions.

## References

[0626] The specification is most thoroughly understood in light of the following references, all of which are hereby incorporated by reference in their entireties. The disclosures of the patents and other references cited above are also hereby incorporated by reference.

1. Agou, F., Quevillon, S., Kerjan, P., Latreille, M.T., Mirande, M. (1996) Functional replacement of hamster lysyl-tRNA synthetase by the yeast enzyme requires cognate amino acid sequences for proper tRNA recognition. *Biochemistry* 35:15322-15331.
2. Agrawal, S., Crooke, S.T. eds. (1998) Antisense Research and Application (Handbook of Experimental Pharmacology, Vol 131). Springer-Verlag New York, Inc.
3. Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J.D. (1994) Molecular Biology of the Cell. 3<sup>rd</sup> ed. Garland Publishing, Inc.
4. Alexander, D.R. (2000) The CD45 tyrosine phosphatase: a positive and negative regulator of immune cell function. *Semin. Immunol* 12:349-359.
5. Allison, A.C. (2000) Immunosuppressive drugs: the first 50 years and a glance forward. *Immunopharmacology* 47:63-83.
6. Altschul, S.F., Gish, W., Miller, W., Myers, E.W., Lipman, D.J. (1990) Basic alignment search tool. *J. Mol. Biol.* 215:403-410.
7. Altschul, S.F., Madden, T.L., Schäffer, A.A., Zhang, J., Zheng, Z., Miller, W., Lipman, D.J. (1997) Gapped BLAST and PSI-BLAST: a new generation of protein database search programs. *Nucleic Acids Res.* 25:3389-3402.
8. Amor, J.C., Harrison, D.H., Kahn, R.A., Ringe, D. (1994) Structure of the human ADP-ribosylation factor 1 complexed with GDP. *Nature* 372:704-708.
9. Andreeff, M., Pinkel, D. eds. (1999) Introduction to Fluorescence In Situ Hybridization: Principles and Clinical Applications. John Wiley & Sons.
10. Andres, D.A., Shao, H., Crick, D.C., Finlin, B.S. (1997) Expression cloning of a novel farnesylated protein, RDJ2, encoding a DnaJ protein homologue. *Arch. Biochem. Biophys.* 346:113-124.
11. Ansel, H.C., Allen, L., Popovich, N.G. eds. (1999) Pharmaceutical Dosage Forms and Drug Delivery Systems. 7<sup>th</sup> ed. Lippencott Williams and Wilkins Publishers.

12. Aubry, M., Marineau, C., Zhang, F.R., Zahed, L., Figlewicz, D., Delattre, O., Thomas, G., de Jong, P.J., Julien, J.P., Rouleau, G.A. (1992) Cloning of six new genes with zinc finger motifs mapping to short and long arms of human acrocentric chromosome 22 (p and q11.2). *Genomics* 13:641-648.
13. Ausubel, F., Brent, R., Kingston, R.E., Moore, D.D., Seidman, J.G., Smith, J.A., eds. (1999) Short Protocols in Molecular Biology. 4<sup>th</sup> ed. Wiley & Sons.
14. Baksh, S., Burakoff, S.J. (2000) The role of calcineurin in lymphocyte activation. *Semin. Immunol.* 12:405-415.
15. Ballance, D.J., Buxton, F.P., Turner, G. (1983) Transformation of *Aspergillus nidulans* by the orotidine-5'-phosphate decarboxylase gene of *Neurospora crassa*. *Biochem. Biophys. Res. Commun.* 112:284-289.
16. Barany, F. (1985) Single-stranded hexameric linkers: a system for in-phase insertion mutagenesis and protein engineering. *Gene* 37:111-123.
17. Barnes, D., Sato, G. (1980) Methods for growth of cultured cells in serum-free medium. *Anal. Biochem.* 102:255-270.
18. Barton, M.C., Hoekstra, M.F., Emerson, B.M. (1990) Site-directed, recombination-mediated mutagenesis of a complex gene locus. *Nucleic Acids Res.* 18:7349-7355.
19. Bashkin, J.K., Sampath, U., Frolova, E. (1995) Ribozyme mimics as catalytic antisense reagents. *Appl. Biochem. Biotechnol.* 54:43-56.
20. Bassett, D.E., Eisen, M.B., Boguski, M.S. (1999) Gene expression informatics - it's all in your mine. *Nature Genetics* 21:51-55.
21. Bast, R.C., Kufe, D.W., Pollock, R.E., Weichselbaum, R.R., Holland, J.F., Frei, E., eds. (2000) Cancer Medicine. 5th ed. B.C. Decker, Inc.
22. Bateman, A., Birney, E., Cerruti, L., Durbin, R., Etwiller, L., Eddy, S.R., Griffiths-Jones, S., Howe, K.L., Marshall, M., Sonnhammer, E.L.L. (2000) *Nucleic Acids Research* 30:276-280.
23. Battini, R., Ferrari, S., Kaczmarek, L., Calabretta, B., Chen, S.T., Baserga, R. (1987) Molecular cloning of a cDNA for a human ADP/ATP carrier which is growth-regulated. *J. Biol. Chem.* 262:4355-4359.
24. Beach, D., Durkacz, B., Nurse, P. (1982) Functionally homologous cell cycle control genes in budding and fission yeast. *Nature* 300:706-709.

25. Beigelman, L., Karpeisky, A., Matulic-Adamic, J., Haeberli, P., Sweedler, D., Usman, N. (1995) Synthesis of 2'-modified nucleotides and their incorporation into hammerhead ribozymes. *Nucleic Acids Res.* 23:4434-4442.
26. Bennett, J. (2000) Gene therapy for retinitis pigmentosa. *Curr. Opin. Mol. Ther.* 2:420-425.
27. Berinstein, N.L. (2002) Carcinoembryonic antigen as a target for therapeutic anti-cancer vaccines: a review. *J. Clin. Oncol.* 20:2197-2207.
28. Bibikova, M., Beumer, K., Trautman, J.K., Carroll, D. (2003) Enhancing gene targeting with designed zinc finger nucleases. *Science* 300:764.
29. Birney, E., Durbin, R. (2000) Using GeneWise in the *Drosophila* annotation experiment. *Genome Res.* 10:547-548.
30. Blackwell, J.M., Barton, C.H., White, J.K., Searle, S., Baker, A.M., Williams, H., Shaw, M.A. (1995) Genomic organization and sequence of the human NRAMP gene: identification and mapping of a promoter region polymorphism. *Mol. Med.* 1:194-205.
31. Bodzioch, M., Orso, E., Klucken, J., Langmann, T., Bottcher, A., Diederich, W., Drobnik, W., Barlage, S., Buchler, C., Porsch-Ozcurumez, M., Kaminski, W.E., Hahmann, H.W., Oette, K., Rothe, G., Aslanidis, C., Lackner, K.J., Schmitz, G. (1999) The gene encoding ATP-binding cassette transporter 1 is mutated in Tangier disease. *Nat. Genet.* 1999 22:347-351.
32. Bonifaci, N., Moroiaru, J., Radu, A., Blobel, G. (1997) Karyopherin beta2 mediates nuclear import of a mRNA binding protein. *Proc. Natl. Acad. Sci.* 94:5055-5060.
33. Bono, H., Kasukawa, T., Furuno, M., Hayashizaki, Y., Okazaki, Y. (2002) FANTOM DB: database of Functional Annotation of RIKEN Mouse cDNA Clones. *Nucleic Acids Res.* 30:116-118.
34. Boshart, M., Weber, F., Jahn, G., Dorsch-Hasler, K., Fleckenstein, B., Schaffner, W. (1985) A very strong enhancer is located upstream of an immediate early gene of human cytomegalovirus. *Cell* 41:521-530.
35. Bowtell, D.D.L. (1999) Options available - from start to finish - for obtaining expression data by microarray. *Nature Genetics* 21:25-32.
36. Brenner, S., Williams, S.R., Vermass, E.H., Storck, T., Moon, K., McCollum, C., Mao, J.I., Luo, S., Kirchner, J.J., Eletr, S., DuBridge, R.B., Burcham, T., Albrecht, G. (2000) *In vitro* cloning of complex mixtures of DNA on

- microbeads: physical separation of differentially expressed cDNAs. *Proc. Natl. Acad. Sci. USA* 97:1665-1670.
37. Brock, G. (2000) Sildenafil citrate (Viagra®). *Drugs Today* 36:125-134.
38. Brown, J.R., Daar, I.O., Krug, J.R., Maquat, L.E. (1985) Characterization of the functional gene and several processed pseudogenes in the human triosephosphate isomerase gene family. *Mol. Cell Biol.* 5:1694-1706.
39. Brown, P.O., Botstein, D. (1999) Exploring the new world of the genome with DNA microarrays. *Nature Genetics* 21:33-37.
40. Brunelleschi, S., Penengo, L., Santoro, M.M., Gaudino, G. (2002) Receptor tyrosine kinases as target for anti-cancer therapy. *Curr. Pharm. Des.* 8:1959-1972.
41. Brutlag, D.L., Dautricourt, J.P., Diaz, R., Fier, J., Moxon, B., Stamm, R. (1993). BLAZE: An implementation of the Smith-Waterman comparison algorithm on a massively parallel computer. *Computers and Chemistry* 17:203-207.
42. Carbonell, L.F., Hodge, M.R., Tomalski, M.D., Miller, L.K. (1988) Synthesis of a gene coding for an insect-specific scorpion neurotoxin and attempts to express it using baculovirus vectors. *Gene* 73:409-418.
43. Chakravarty, A. (1999) Population genetics - making sense out of sequence. *Nature Genetics* 21:56-60.
44. Chalifour, L.E., Fahmy, R., Holder, E.L., Hutchinson, E.W., Osterland, C.K., Schipper, H.M., Wang, E. (1994) A method for analysis of gene expression patterns. *Anal. Biochem.* 216: 299-304.
45. Chalut, C., Gallois, Y., Poterszman, A., Moncollin, V., Egly, J.M. (1995) Genomic structure of the human TATA-box-binding protein (TBP). *Gene* 161:277-282.
46. Chang, A.C., Nunberg, J.H., Kaufman, R.J., Erlich, H.A., Schimke, R.T., Cohen, S.N. (1978) Phenotypic expression in *E. coli* of a DNA sequence coding for mouse dihydrofolate reductase. *Nature* 275:617-624.
47. Chang, M.S., Chang, C.L., Huang, C.J., Yang, Y.C. (2000) p29, a novel GCIP-interacting protein, localizes in the nucleus. *Biochem. Biophys. Res. Commun.* 279:732-737.
48. Chen, F.W., Ioannou, Y.A. (1998) Ribosomal proteins in cell proliferation and apoptosis. *Int. Rev. Immunol.* 18:429-448.

49. Chen, S.Y., Bagley, J., Marasco, W.A. (1994) Intracellular antibodies as a new class of therapeutic molecule for gene therapy. *Hum. Gene Ther.* 5:595-601.
50. Cheng, W.F., Hung, C.F., Chai, C.Y., Hsu, K.F., He, L., Ling, M., Wu, T.C. (2001) Tumor-specific immunity and angiogenesis generated by a DNA vaccine encoding calreticulin linked to a tumor antigen. *J. Clin. Invest.* 108:669-678.
51. Cheung, V.G., Morley, M., Aquilar, F., Massimi, A., Kucherlapati, R., Childs, G. (1999) Making and reading microarrays. *Nature Genetics* 21:15-19.
52. Chien, C., Bartel, P.L., Sternglanz, R., Fields S. (1991) The two-hybrid system: A method to identify and clone genes for proteins that interact with a protein of interest. *Proc. Natl. Acad. Sci.* 88:9578-9581.
53. Christa, L., Simon, M.T., Flinois, J.P., Gebhardt, R., Brechot, C., Lasserre, C. (1994) Overexpression of glutamine synthetase in human primary liver cancer. *Gastroenterology* 106:1312-1320.
54. Clark, C.M., Karlawish, J.H. (2003) Alzheimer disease: current concepts and emerging diagnostic and therapeutic strategies. *Ann. Intern. Med.* 138:400-410.
55. Coffin, J.M., Hughes, S.H., Varmus, H.E. (1997) Retroviruses. Cold Spring Harbor Laboratory Press.
56. Cole, K.A., Krizman, D.B., Emmert-Buck, M.R. (1999) The genetics of cancer - a 3D model. *Nature Genetics* 21:38-41.
57. Colicelli, J., Lobel, L.I., Goff, S.P. (1985) A temperature-sensitive mutation constructed by "linker insertion" mutagenesis. *Mol. Gen. Genet.* 199:537-539.
58. Collins, F.S. (1999) Microarrays and macroconsequences. *Nature Genetics* 21:2.
59. Comuzzie, A.G., Allison, D.B. (1998) The search for human obesity genes. *Science* 280:1374-1377.
60. Cormand, B., Montfort, M., Chabas, A., Vilageliu, L., Grinberg, D. (1997) Genetic fine localization of the beta-glucocerebrosidase (GBA) and prosaposin (PSAP) genes: implications for Gaucher disease. *Hum. Genet.* 100:75-79.
61. Cregg, J.M., Barringer, K.J., Hessler, A.Y., Madden, K.R. (1985) *Pichia pastoris* as a host system for transformations. *Mol. Cell. Biol.* 5:3376-3385.



62. Crooke, S.T. (1996) Progress in antisense therapeutics. *Med. Res. Rev.* 16:319-344.
63. Crouch, R.J. (1990) Ribonuclease H: from discovery to 3D structure. *New Biol.* 2:771-777.
64. Curcio, L.D., Bouffard, D.Y., Scanlon, K.J. (1997) Oligonucleotides as modulators of cancer gene expression. *Pharmacol. Ther.* 74:317-332.
65. Das, S., Kellermann, E., Hollenberg, C.P. (1984) Transformation of *Kluyveromyces fragilis*. *J. Bacteriol.* 158:1165-1167.
66. Davidow, L.S., Kaczmarek, F.S., DeZeeuw, J.R., Conlon, S.W., Lauth, M.R., Pereira, D.A., Franke, A.E. (1987) The Yarrowia lipolytica LEU2 gene. *Curr. Genet.* 11:377-383.
67. de Boer, H.A., Comstock, L.J., Vasser, M. (1993) The tac promoter: a functional hybrid derived from the trp and lac promoters. *Proc. Natl. Acad. Sci.* 80:21-25.
68. De Louvencourt, L., Fukuhara, H., Heslot, H., Wesolowski, M. (1983) Transformation of *Kluyveromyces lactis* by killer plasmid DNA. *J. Bacteriol.* 154:737-742.
69. Deasy, B.M., Huard, J. (2002) Gene therapy and tissue engineering based on muscle-derived stem cells. *Curr. Opin. Mol. Ther.* 4:382-389.
70. Delahunty, C., Ankener, W., Deng, Q., Eng, J., Nickerson, D.A. (1996) Testing the feasibility of DNA typing for human identification by PCR and an oligonucleotide ligation assay. *Am. J. Human Genetics* 58:1239-1246.
71. Deutscher, M.P., Simon, M.I., Abelson, J.N., eds. (1990) Guide to Protein Purification: Methods in Enzymology. (Methods in Enzymology Series, Vol 182). Academic Press.
72. Dieffenbach, C.W., Dveksler, G.S., eds. (1995) PCR Primer: A Laboratory Manual. Cold Spring Harbor Laboratory Press.
73. Dijkema, R., van der Meide, P.H., Pouwels, P.H., Caspers, M., Dubbeld, M., Schellekens, H. (1985) Cloning and expression of the chromosomal immune interferon gene of the rat. *EMBO J.* 4:761-767.
74. Doerfler, W., Bohm, P., eds. (1987) The Molecular Biology Of Baculoviruses. Springer-Verlag, Inc.

75. Doll, A., Grzeschik, K.H. (2001) Characterization of two novel genes, WBSCR20 and WBSCR22, deleted in Williams-Beuren syndrome. *Cytogenet. Cell Genet.* 95:20-27.
76. Doolittle, R.F., Abelson, J.N., Simon, M.I., eds. (1996) Computer Methods for Macromolecular Sequence Analysis. 1st ed. Academic Press.
77. Ducrest, A.L., Suzutorisz, H., Lingner, J., Nabholz, M. (2002) Regulation of the human telomerase reverse transcriptase gene. *Oncogene* 21:541-52.
78. Dutoit, V., Taub, R.N., Papadopoulos, K.P., Talbot, S., Keohan, M.L., Brehm, M., Gnjatich, S., Harris, P.E., Bisikirska, B., Guillaume, P., Cerottini, J.C., Hesdorffer, C.S., Old, L.J., Valmori, D. (2002) Multiepitope CD8<sup>+</sup> T cell response to an NY-ESO-1 peptide vaccine results in imprecise tumor targeting. *J. Clin. Invest.* 110:1813-1822.
79. Egilsson, V., Gudnason, V., Jonasdottir, A., Ingvarsson, S., Andresdottir, V. (1986) Catabolite repressive effects of 5-thio-D-glucose on *Saccharomyces cerevisiae*. *J. Gen. Microbiol.* 132:3309-3313.
80. Ehrhardt, G.R., Korherr, C., Wieler, J.S., Knaus, M., Schrader, J.W. (2001) A novel potential effector of M-Ras and p21 Ras negatively regulates p21 Ras-mediated gene induction and cell growth. *Oncogene* 20:188-197.
81. Espejo, A., Cote, J., Bednarek, A., Richard, S., Bedford, M.T. (2002) A protein-domain microarray identifies novel protein-protein interactions. *Biochem. J.* 367:697-702.
82. Everett, R.D., Meredith, M., Orr, A., Cross, A., Kathoria, M., Parkinson, J. (1997) A novel ubiquitin-specific protease is dynamically associated with the PML nuclear domain and binds to a herpesvirus regulatory protein. *EMBO J.* 16:1519-1530.
83. Fanning, A.S., Anderson, J.M. (1999) Protein modules as organizers of membrane structure. *Curr. Opin. Cell Biol.* 11:432-439.
84. Fields, S., Song, O. (1989) A novel genetic system to detect protein-protein interactions. *Nature* 340:245-246.
85. Fisch, P., Forster, A., Sherrington, P.D., Dyer, M.J., Rabbitts, T.H. (1993) The chromosomal translocation t(X;14)(q28;q11) in T-cell pro-lymphocytic leukaemia breaks within one gene and activates another. *Oncogene* 8:3271-3276.

86. Fishman, P.S., Oyler, G.A. (2002) Significance of the parkin gene and protein in understanding Parkinson's disease. *Curr. Neurol. Neurosci. Rep.* 2:296-302.
87. Forgac, M. (1999) Structure and properties of the vacuolar (H<sup>+</sup>)-ATPases. *J. Biol. Chem.* 274:12,951-12,954.
88. Frank, I. (2002) Antivirals against HIV-1. *Clin. Lab. Med.* 22:741-757.
89. Frithz, G., Ericsson, P., Ronquist, G. (1976) Serum adenylate kinase activity in the early phase of acute myocardial infarction. *Ups J Med Sci.* 81:155-158.
90. Funakoshi, I., Kato, H., Horie, K., Yano, T., Hori, Y., Kobayashi, H., Inoue, T., Suzuki, H., Fukui, S., Tsukahara, M., et al. (1992) Molecular cloning of cDNAs for human fibroblast nucleotide pyrophosphatase. *Arch. Biochem. Biophys.* 295:180-187.
91. Furth, P.A., Shamay, A., Wall, R.J., Hennighausen, L. (1992) Gene transfer into somatic tissues by jet injection. *Anal. Biochem.* 205:365-368.
92. Gaillardin, C., Ribet, A.M. (1987) LEU2 directed expression of beta-galactosidase activity and phleomycin resistance in *Yarrowia lipolytica*. *Curr. Genet.* 11:369-375.
93. Gao, X., Nawaz, Z. (2002) Progesterone receptors - animal models and cell signaling in breast cancer: Role of steroid receptor coactivators and corepressors of progesterone receptors in breast cancer. *Breast Cancer Res.* 4:182-186.
94. Gao, Y., Melki, R., Walden, P.D., Lewis, S.A., Ampe, C., Rommelaere, H., Vandekerckhove, J., Cowan, N.J. (1994) A novel cochaperonin that modulates the ATPase activity of cytoplasmic chaperonin. *J. Cell Biol.* 125:989-996.
95. Gaudilliere, B., Shi, Y., Bonni, A. (2002) RNA interference reveals a requirement for MEF2A in activity-dependent neuronal survival. *J. Biol. Chem.* 277:46,442-46,446.
96. Gavrieli, Y., Sherman, Y., Ben-Sasson, S.A. (1992) Identification of programmed cell death *in situ* via specific labeling of nuclear DNA fragmentation. *J. Cell Biol.* 119:493-501.
97. Geffen D.B., Man S. (2002) New drugs for the treatment of cancer, 1990-2001. *Isr. Med. Assoc. J.* 4:1124-31.
98. Gennaro, A., ed. (2000) Remington: The Science and Practice of Pharmacy. 20th ed. Lippincott, Williams, & Wilkins.

99. Ghotrani, H.A., Rose, F., Schermuly, R.T., Olschewski, H., Wiedemann, R., Kreckel, A., Weissmann, N., Ghotrani, S., Enke, B., Seeger, W., Grimminger, F. (2003) Oral sildenafil as long-term adjunct therapy to inhaled iloprost in severe pulmonary arterial hypertension. *J. Am. Coll. Cardiol.* 42:158-164.
100. Gillingham, A.K., Pfeifer, A.C., Munro, S. (2002) CASP, the alternatively spliced product of the gene encoding the CCAAT-displacement protein transcription factor, is a Golgi membrane protein related to giantin. *Mol. Biol. Cell* 13:3761-3774.
101. Gingras, M.C., Lapillonne, H., Margolin, J.F. (2002) TREM-1, MDL-1, and DAP12 expression is associated with a mature stage of myeloid development. *Mol. Immunol.* 38:817-824.
102. Girschick, H.J., Grammer, A.C., Nanki, T., Vazquez, E., Lipsky, P.E. (2002) Expression of recombination activating genes 1 and 2 in peripheral B cells of patients with systemic lupus erythematosus. *Arthritis. Rheum.* 46:1255-1263.
103. Gmeiner, W.H., Horita, D.A. (2001) Implications of SH3 domain structure and dynamics for protein regulation and drug design. *Cell Biochem. Biophys.* 35:127-140.
104. Goeddel, D.V., Heyneker, H.L., Hozumi, T., Arentzen, R., Itakura, K., Yansura, D.G., Ross, M.J., Mizzari, G., Crea, R., Seeburg, P.H. (1979) Direct expression in *E. coli* of a DNA sequence coding for human growth hormone. *Nature* 281:544-548.
105. Goldstein, L.S.B., Yang, Z. (2000) Microtubule-based transport systems in neurons: the roles of kinesins and dyneins. *Annu. Rev. Neurosci.* 23:39-71.
106. Golovkina, T.V., Chervonsky, A., Dudley, J.P., Ross, S.R. (1992) Transgenic mouse mammary tumor virus superantigen expression prevents viral infection. *Cell* 69:637-645.
107. Gonnet, G.H., Cohen, M.A., Benner, S.A. (1992) Exhaustive matching of the entire protein sequence database. *Science* 256:1443-1445.
108. Gordan, J.D., Vonderheide, R.H. (2002) Universal tumor antigens as targets for immunotherapy. *Cytotherapy* 4:317-327.
109. Gorman, C.M., Merlino, G.T., Willingham, M.C., Pastan, I., Howard, B.H. (1982) The Rous sarcoma virus long terminal repeat is a strong

- promoter when introduced into a variety of eucaryotic cells by DNA-mediated transfection. *Proc. Natl. Acad. Sci.* 79:6777-6781.
110. Gray, T.A., Hernandez, L., Carey, A.H., Schaldach, M.A., Smithwick, M.J., Rus, K.M., Graves, J.A., Stewart, C.L., Nicholls, R.D. (2002) The ancient source of a distinct gene family encoding proteins featuring RING and C(3)H zinc-finger motifs with abundant expression in developing brain and nervous system. *Genomics.* 66:76-86.
111. Griffiths, A.J.F., Miller, J.H., Suzuki, D.T., Lewontin, R.C., Gelbart, W.M. (1999) Introduction to Genetic Analysis. 7<sup>th</sup> ed. W.H. Freeman.
112. Griffiths, M., Beaumont, N., Yao, S.Y., Sundaram, M., Boumah, C.E., Davies, A., Kwong, F.Y., Coe, I., Cass, C.E., Young, J.D., Baldwin, S.A. (1997) Cloning of a human nucleoside transporter implicated in the cellular uptake of adenosine and chemotherapeutic drugs. *Nat. Med.* 3:89-93.
113. Grosschedl, R., Baltimore, D. (1985) Cell-type specificity of immunoglobulin gene expression is regulated by at least three DNA sequence elements. *Cell* 41:885-897.
114. Grosveld, F., Kollias, G., eds. (1992) Transgenic Animals. 1<sup>st</sup> ed. Academic Press.
115. Gustin, K., Burk, R.D. (1993) A rapid method for generating linker scanning mutants utilizing PCR. *Biotechniques* 14:22-24.
116. Hacia, J.G. (1999) Resequencing and mutational analysis using oligonucleotide microarrays. *Nature Genetics* 21:42-47.
117. Hadano, S., Yanagisawa, Y., Skaug, J., Fichter, K., Nasir, J., Martindale, D., Koop, B.F., Scherer, S.W., Nicholson, D.W., Rouleau, G.A., Ikeda, J., Hayden, M.R. (2001) Cloning and characterization of three novel genes, ALS2CR1, ALS2CR2, and ALS2CR3, in the juvenile amyotrophic lateral sclerosis (ALS2) critical region at chromosome 2q33-q34: candidate genes for ALS2. *Genomics* 71:200-213.
118. Hall, M., Mickey, D.D., Wenger, A.S., Silverman, L.M. (1985) Adenylate kinase: an oncodevelopmental marker in an animal model for human prostatic cancer. *Clin. Chem.* 31:1689-1691.
119. Ham, R.G., McKeehan, W.L. (1979) Media and growth requirements. *Methods Enzymol.* 58:44-93.

120. Hanada, T., Lin, L., Tibaldi, E.V., Reinherz, E.L., Chishti, A.H. (2000) GAKIN, a novel kinesin-like protein associates with the human homologue of the *Drosophila* discs large tumor suppressor in T lymphocytes. *J. Biol. Chem.* 275:28,774-28,784.
121. Harlow, E., Lane, D., eds. (1988) Antibodies: A Laboratory Manual. Cold Spring Harbor Laboratory.
122. Harlow, E., Lane, D., Harlow, E., eds. (1998) Using Antibodies: A Laboratory Manual: Portable Protocol NO. I. Cold Spring Harbor Laboratory.
123. Hartmann, G., Endres, S., eds. (1999) Manual of Antisense Methodology (Perspectives in Antisense Science). 1<sup>st</sup> ed. Kluwer Law International.
124. Hassanzadeh, G.H.G., De Silva, K.S., Dambly-Chudiere, C., Brys, L., Ghysen, A., Hamers, R., Muyldermans, S., De Baetselier, P. (1998) Isolation and characterization of single-chain Fv genes encoding antibodies specific for *Drosophila* Poxn protein. *FEBS Lett.* 437:75-80.
125. Hawes, J.W., Jaskiewicz, J., Shimomura, Y., Huang, B., Bunting, J., Harper, E.T., Harris, R.A. (1996) Primary structure and tissue-specific expression of human beta-hydroxyisobutyryl-coenzyme A hydrolase. *J. Biol. Chem.* 271:26,430-26,434.
126. Heath, J.K., White, S.J., Johnstone, C.N., Catimel, B., Simpson, R.J., Moritz, R.L., Tu, G.F., Ji, H., Whitehead, R.H., Groenen, L.C., Scott, A.M., Ritter, G., Cohen, L., Welt, S., Old, L.J., Nice, E.C., Burgess, A.W. (1997) The human A33 antigen is a transmembrane glycoprotein and a novel member of the immunoglobulin superfamily. *Proc. Natl. Acad. Sci.* 94:469-474.
127. Heiser, A., Coleman, D., Dannull, J., Yancey, D., Maurice, M.A., Lallas, C.D., Dahm, P., Niedzwiecki, D., Gilboa, E., Vieweg, J. (2002) Autologous dendritic cells transfected with prostate-specific antigen RNA stimulate CTL responses against metastatic prostate tumors. *J. Clin. Invest.* 109:409-417.
128. Henningson, C.T. Jr., Stanislaus, M.A., Gewirtz, A.M. (2003) Embryonic and adult stem cell therapy. *J. Allergy Clin. Immunol.* 111:S745-S753.
129. Hinnen, A., Hicks, J.B., Fink, G.R. (1978) Transformation of yeast. *Proc. Natl. Acad. Sci.* 75:1929-1933.

130. Hirsch, D.S., Pirone, D.M., Burbelo, P.D. (2001) A new family of Cdc42 effector proteins, CEPs, function in fibroblast and epithelial cell shape changes. *J. Biol. Chem.* 276:875-883.
131. Ho, L.W., Carmichael, J., Swartz, J., Wyttenbach, A., Rankin, J., Rubinsztein, D.C. (2001) The molecular biology of Huntington's disease. *Psychol. Med.* 31:3-14.
132. Hollis, G.F., Evans, R.J., Stafford-Hollis, J.M., Korsmeyer, S.J., McKearn, J.P. (1989) Immunoglobulin lambda light-chain-related genes 14.1 and 16.1 are expressed in pre-B cells and may encode the human immunoglobulin omega light-chain protein. *Proc. Natl. Acad. Sci.* 86:5552-5556.
133. Hong, G.F. (1982) Sequencing of large double-stranded DNA using the dideoxy sequencing technique. *Biosci. Rep.* 2:907-912.
134. Hoogenboom, H.R., de Bruin, A.P., Hufton, S.E., Hoet, R.M., Arends, J.W., Roovers, R.C. (1998) Antibody phage display technology and its applications. *Immunotechnology* 4:1-20.
135. Hooper, M.L. (1993) Embryonal Stem Cells: Introducing Planned Changes into the Animal Germline. Gordon & Breach Science Pub.
136. Hoozemans, J.J., Veerhuis, R., Rozemuller, A.J., Eikelenboom, P. (2002) The pathological cascade of Alzheimer's disease: the role of inflammation and its therapeutic implications. *Drugs Today (Barc)* 38:429-443.
137. Houseman, B.T., Huh, J.H., Kron, S.J., Mrksich, M. (2002) Peptide chips for the quantitative evaluation of protein kinase activity. *Nature Biotechnol.* 20:270-274.
138. Howard, G.C., Bethell, D.R. (2000) Basic Methods in Antibody Production and Characterization. CRC Press.
139. Huynh, D.P., Yang, H.T., Vakharia, H., Nguyen, D., Pulst, S.M. (2003) Expansion of the polyQ repeat in ataxin-2 alters its Golgi localization, disrupts the Golgi complex and causes cell death. *Hum. Mol. Genet.* 12:1485-1496.
140. Ikeda, A., Nishina, P.M., Naggert, J.K. (2002) The tubby-like proteins, a family with roles in neuronal development and function. *J. Cell Sci.* 115(Pt 1):9-14.

141. Ito, H., Fukuda, Y., Murata, K., Kimura, A. (1978) Transformation of intact yeast cells treated with alkali cations. *J. Bacteriol.* 153:163-168.
142. Jameson, D.M., Sawyer, W.H. (1995) Fluorescence anisotropy applied to biomolecular interactions. *Methods Enzymol.* 246:283-300.
143. Janeway, C.A., Travers, P., Walport, M. Shlomchik, M. (2001) Immunobiology. 5<sup>th</sup> ed. Garland Publishing.
144. Jeffery, P., Zhu, J. (2002) Mucin-producing elements and inflammatory cells. *Novartis Found. Symp.* 248:51-75, 277-82.
145. Jimbo, T., Kawasaki, Y., Koyama, R., Sato, R., Takada, S., Haraguchi, K., Akiyama, T. (2002) Identification of a link between the tumour suppressor APC and the kinesin superfamily. *Nat. Cell Biol.* 4:323-327.
146. Joberty, G., Perlungher, R.R., Macara, I.G. (1999) The Borgs, a new family of Cdc42 and TC10 GTPase-interacting proteins. *Mol. Cell Biol.* 19:6585-6597.
147. Johns, T.G., Bernard, C.C. (1997) Binding of complement component C1q to myelin oligodendrocyte glycoprotein: a novel mechanism for regulating CNS inflammation. *Mol. Immunol.* 34:33-38.
148. Jolliffe, C.N., Harvey, K.F., Haines, B.P., Parasivam, G., Kumar, S. (2000) Identification of multiple proteins expressed in murine embryos as binding partners for the WW domains of the ubiquitin-protein ligase Nedd4. *Biochem. J.* 351:557-565.
149. Jones, D.H., Winistorfer, S.C. (1992) Recombinant circle PCR and recombination PCR for site-specific mutagenesis without PCR product purification. *Biotechniques* 12:528-530.
150. Jones, P., ed. (1998a) Vectors: Cloning Applications: Essential Techniques, John Wiley & Son, Ltd.
151. Jones, P., ed. (1998b) Vectors: Expression Systems: Essential Techniques, John Wiley & Son, Ltd.
152. Jost, C.R., Kurucz I., Jacobus, C.M., Titus, J.A., George, A.J., Segal, D.M. (1994) Mammalian expression and secretion of functional single-chain Fv molecules. *J. Biol. Chem.* 269:26,267-26,273.
153. Joulin, V., Richard-Foy, H. (1995) A new approach to isolate genomic control regions. Application to the GATA transcription factor family. *Eur. J. Biochem.* 232:620-626.



154. Jurcic, J.G., Cathcart, K., Pinilla-Ibarz, J., Scheinberg, D.A. (2000) Advances in immunotherapy of hematologic malignancies: cellular and humoral approaches. *Curr. Opin. Hematol.* 7:247-254.
155. Jury, J.A., Perry, A.C., Hall, L. (1999) Identification, sequence analysis and expression of transcripts encoding a putative metalloproteinase, eMDC II, in human and macaque epididymis. *Mol. Hum. Reprod.* 5:1127-1134.
156. Kabat, E.A., Wu T.T. (1991) Identical V region amino acid sequences and segments of sequences in antibodies of different specificities. Relative contributions of VH and VL genes, minigenes, and complementarity-determining regions to binding of antibody-combining sites. *J. Immunol.* 147:1709-1719.
157. Kamitani, T., Nguyen, H.P., Yeh, E.T. (1997) Preferential modification of nuclear proteins by a novel ubiquitin-like molecule. *J. Biol. Chem.* 272:14,001-14,004.
158. Kantoff, P.W., Halabi, S., Farmer, D.A., Hayes, D.F., Vogelzang, N.A., Small, E.J. (2001) Prognostic significance of reverse transcriptase polymerase chain reaction for prostate-specific antigen in men with hormone-refractory prostate cancer. *J. Clin. Oncol.* 9:3025-3028.
159. Kao, P.N., Chen, L., Brock, G., Ng, J., Kenny, J., Smith, A.J., Cortesy, B. (1994) Cloning and expression of cyclosporin A- and FK506-sensitive nuclear factor of activated T-cells: NF45 and NF90. *J. Biol. Chem.* 269:20,691-20,699.
160. Karanazashvili, G., Abrahamsson, P. (2003) Prostate specific antigen and human glandular kallikrein 2 in early detection of prostate cancer. *J. Urol.* 169:445-457.
161. Kari, C., Chan, T.O., Rocha de Quadros, M., Rodeck, U. (2003) Targeting the epidermal growth factor receptor in cancer: apoptosis takes center stage. *Cancer Res.* 63:1-5.
162. Kelly, J.M., Hynes, M.J. (1985) Transformation of *Aspergillus niger* by the mdS gene of *Aspergillus nidulans*. *EMBO J.* 4:475-479.
163. Kenmochi, N., Kawaguchi, T., Rozen, S., Davis, E., Goodman, N., Hudson, T.J., Tanaka, T., Page, D.C. (1998) A map of 75 human ribosomal protein genes. *Genome Res.* 8:509-523.

164. Keown, W.A., Campbell, C.R., Kucherlapati, R.S. (1990) Methods for introducing DNA into mammalian cells. *Methods Enzymol.* 185:527-537.
165. Kibbe, A.H., ed. (2000) Handbook of Pharmaceutical Excipients. 3<sup>rd</sup> ed. Pharmaceutical Press.
166. Kirkpatrick, K.L., Mokbel, K. (2001) The significance of human telomerase reverse transcriptase (hTERT) in cancer. *Eur. J. Surg. Oncol.* 27:754-760.
167. Kirsch, K.H., Georgescu, M.M., Ishimaru, S., Hanafusa, H. (1999) CMS: an adapter molecule involved in cytoskeletal rearrangements. *Proc. Natl. Acad. Sci.* 96:6211-6216.
168. Kiryu-Seo, S., Sasaki, M., Yokohama, H., Nakagomi, S., Hirayama, T., Aoki, S., Wada, K., Kiyama, H. (2000) Damage-induced neuronal endopeptidase (DINE) is a unique metallopeptidase expressed in response to neuronal damage and activates superoxide scavengers. *Proc. Natl. Acad. Sci.* 97:4345-4350.
169. Klarman, G.J., Hawkins, M.E., Le Grice, S.F. (2002) Uncovering the complexities of retroviral ribonuclease H reveals its potential as a therapeutic target. *AIDS Rev.* 4:183-194.
170. Knutson, K.L., Schiffman, K., Disis, M.L. (2001) Immunization with a HER-2/neu helper peptide vaccine generates HER-2/neu CD8 T-cell immunity in cancer patients. *J. Clin. Invest.* 107:477-484.
171. Kobayashi, M., Takezawa, S., Hara, K., Yu, R.T., Umesono, Y., Agata, K., Taniwaki, M., Yasuda, K., Umesono, K. (1999) Identification of a photoreceptor cell-specific nuclear receptor. *Proc. Natl. Acad. Sci.* 96:4814-4819.
172. Kolonin, M.G., Finley, R.L. Jr. (1998) Targeting cyclin-dependent kinases in *Drosophila* with peptide aptamers. *Proc. Natl. Acad. Sci.* 95:14,266-14,271.
173. Korner, C., Knauer, R., Stephani, U., Marquardt, T., Lehle, L., von Figura, K. (1999) Carbohydrate deficient glycoprotein syndrome type IV: deficiency of dolichyl-P-Man:Man(5)GlcNAc(2)-PP-dolichyl mannosyltransferase. *EMBO J.* 18:6816-6822.
174. Kothapalli, R., Buyuksal, I., Wu, S.Q., Chegini, N., Tabibzadeh, S. (1997) Detection of ebaf, a novel human gene of the transforming growth

- factor beta superfamily association of gene expression with endometrial bleeding. *J. Clin. Invest.* 99:2342-2350.
175. Kovalenko, O.V., Golub, E.I., Bray-Ward, P., Ward, D.C., Radding, C.M. (1997) A novel nucleic acid-binding protein that interacts with human rad51 recombinase. *Nucleic Acids Res.* 25:4946-4953.
176. Kratzschmar, J., Lum, L., Blobel, C.P. (1996) Metargidin, a membrane-anchored metalloprotease-disintegrin protein with an RGD integrin binding sequence. *J. Biol. Chem.* 271:4593-4596.
177. Ku, D.H., Kagan, J., Chen, S.T., Chang, C.D., Baserga, R., Wurzel, J. (1990) The human fibroblast adenine nucleotide translocator gene. Molecular cloning and sequence. *J. Biol. Chem.* 265:16,060-16,063.
178. Kuisle, O., Quiñó, E., Rigura, R. (1999) Solid phase synthesis of depsides and depsipeptides. *Tetrahedron Lett.* 40:1203-1206.
179. Kunze, G. et al., (1985) Transformation of the industrially important yeasts *Candida maltosa* and *Pichia guilliermondii*. *J. Basic Microbiol.* 25:141-144.
180. Kurtz, M.B., Cortelyou, M.W., Kirsch, D.R. (1986) Integrative transformation of *Candida albicans*, using a cloned *Candida* ADE2 gene. *Mol. Cell. Biol.* 6:142-149.
181. Kyo, S., Takakura, M., Inoue, M. (2000) Telomerase activity in cancer as a diagnostic and therapeutic target. *Histol. Histopathol.* 15:813-824.
182. Lander, E.S. (1999) Array of hope. *Nature Genetics* 21:3-4.
183. Lander, E.S., Linton, L.M., Birren, B., Nusbaum, C., Zody, M.C., Baldwin, J., Devon, K., Dewar, K., Doyle, M., FitzHugh, W., Funke, R., Gage, D., Harris, K., Heaford, A., Howland, J., Kann, L., Lehoczky, J., LeVine, R., McEwan, P., McKernan, K., Meldrim, J., Mesirov, J.P., Miranda, C., Morris, W., Naylor, J., Raymond, C., Rosetti, M., Santos, R., Sheridan, A., Sougnez, C., Stange-Thomann, N., Stojanovic, N., Subramanian, A., Wyman, D., Rogers, J., Sulston, J., Ainscough, R., Beck, S., Bentley, D., Burton, J., Clee, C., Carter, N., Coulson, A., Deadman, R., Deloukas, P., Dunham, A., Dunham, I., Durbin, R., French, L., Grafham, D., Gregory, S., Hubbard, T., Humphray, S., Hunt, A., Jones, M., Lloyd, C., McMurray, A., Matthews, L., Mercer, S., Milne, S., Mullikin, J.C., Mungall, A., Plumb, R., Ross, M.,

Shownkeen, R., Sims, S., Waterston, R.H., Wilson, R.K., Hillier, L.W., McPherson, J.D., Marra, M.A., Mardis, E.R., Fulton, L.A., Chinwalla, A.T., Pepin, K.H., Gish, W.R., Chissoe, S.L., Wendl, M.C., Delehaunty, K.D., Miner, T.L., Delehaunty, A., Kramer, J.B., Cook, L.L., Fulton, R.S., Johnson, D.L., Minx, P.J., Clifton, S.W., Hawkins, T., Branscomb, E., Predki, P., Richardson, P., Wenning, S., Slezak, T., Doggett, N., Cheng, J.F., Olsen, A., Lucas, S., Elkin, C., Uberbacher, E., Frazier, M., Gibbs, R.A., Muzny, D.M., Scherer, S.E., Bouck, J.B., Sodergren, E.J., Worley, K.C., Rives, C.M., Gorrell, J.H., Metzker, M.L., Naylor, S.L., Kucherlapati, R.S., Nelson, D.L., Weinstock, G.M., Sakaki, Y., Fujiyama, A., Hattori, M., Yada, T., Toyoda, A., Itoh, T., Kawagoe, C., Watanabe, H., Totoki, Y., Taylor, T., Weissenbach, J., Heilig, R., Saurin, W., Artiguenave, F., Brottier, P., Bruls, T., Pelletier, E., Robert, C., Wincker, P., Smith, D.R., Doucette-Stamm, L., Rubenfield, M., Weinstock, K., Lee, H.M., Dubois, J., Rosenthal, A., Platzer, M., Nyakatura, G., Taudien, S., Rump, A., Yang, H., Yu, J., Wang, J., Huang, G., Gu, J., Hood, L., Rowen, L., Madan, A., Qin, S., Davis, R.W., Federspiel, N.A., Abola, A.P., Proctor, M.J., Myers, R.M., Schmutz, J., Dickson, M., Grimwood, J., Cox, D.R., Olson, M.V., Kaul, R., Raymond, C., Shimizu, N., Kawasaki, K., Minoshima, S., Evans, G.A., Athanasiou, M., Schultz, R., Roe, B.A., Chen, F., Pan, H., Ramser, J., Lehrach, H., Reinhardt, R., McCombie, W.R., de la Bastide, M., Dedhia, N., Blocker, H., Hornischer, K., Nordsiek, G., Agarwala, R., Aravind, L., Bailey, J.A., Bateman, A., Batzoglu, S., Birney, E., Bork, P., Brown, D.G., Burge, C.B., Cerutti, L., Chen, H.C., Church, D., Clamp, M., Copley, R.R., Doerks, T., Eddy, S.R., Eichler, E.E., Furey, T.S., Galagan, J., Gilbert, J.G., Harmon, C., Hayashizaki, Y., Haussler, D., Hermjakob, H., Hokamp, K., Jang, W., Johnson, L.S., Jones, T.A., Kasif, S., Kasprzyk, A., Kennedy, S., Kent, W.J., Kitts, P., Koonin, E.V., Korf, I., Kulp, D., Lancet, D., Lowe, T.M., McLysaght, A., Mikkelsen, T., Moran, J.V., Mulder, N., Pollara, V.J., Ponting, C.P., Schuler, G., Schultz, J., Slater, G., Smit, A.F., Stupka, E., Szustakowski, J., Thierry-Mieg, D., Thierry-Mieg, J., Wagner, L., Wallis, J., Wheeler, R., Williams, A., Wolf, Y.I., Wolfe, K.H., Yang, S.P., Yeh, R.F., Collins, F., Guyer, M.S., Peterson, J., Felsenfeld, A., Wetterstrand, K.A., Patrinos, A., Morgan, M.J., Szustakowski, J., de Jong, P., Catanese, J.J., Osoegawa, K., Shizuya, H., Choi, S., Chen, Y.J.; International

- Human Genome Sequencing Consortium. (2001) Initial sequencing and analysis of the human genome *Nature* 409:860-921.
184. Lasham, A., Moloney, S., Hale, T., Homer, C., Zhang, Y.F., Murison, J.G., Braithwaite, A.W., Watson, J. (2003) The Y-box binding protein YB1: A potential negative regulator of the p53 tumor suppressor. *J. Biol. Chem.* Epub ahead of print, June 30, 2003.
185. Lashkari, A., Smith, A.K., Graham, J.M. Jr. (1999) Williams-Beuren syndrome: an update and review for the primary physician. *Clin. Pediatr.* 38:189-208.
186. Lavedan, C. (1998) The synuclein family. *Genome Res.* 8:871-880.
187. Lebacqz-Verheyden, A.M., Kasprzyk, P.G., Raum, M.G., Van Wyke Coelingh, K., Lebacqz, J.A., Battey, J.F. (1988) Posttranslational processing of endogenous and of baculovirus-expressed human gastrin-releasing peptide precursor. *Mol. Cell. Biol.* 8:3129-3135.
188. Lees-Miller, S.P., Anderson, C.W. (1989) Two human 90-kDa heat-shock proteins are phosphorylated *in vivo* at conserved serines that are phosphorylated *in vitro* by casein kinase II. *J. Biol. Chem.* 264:2431-2437.
189. Lerch, M.M., Gorelick, F.S. (2000) Early trypsinogen activation in acute pancreatitis. *Med. Clin. North Amer.* 84:549-563.
190. Lerner, R.A. (1982) Tapping the immunological repertoire to produce antibodies of predetermined specificity. *Nature* 299:592-596.
191. Li, E., Bestagno, M., Burrone, O. (1996) Molecular cloning and characterization of a transmembrane surface antigen in human cells. *J. Biochem.* 238:631-638.
192. Lim, D., Orlova, M., Goff, S.P. (Aug. 2002) Mutations of the RNase H C helix of the Moloney murine leukemia virus reverse transcriptase reveal defects in polypurine tract recognition. *J. Virol.* 76:8360-8373.
193. Lin, B., Rommens, J.M., Graham, R.K., Kalchman, M., MacDonald, H., Nasir, J., Delaney, A., Goldberg, Y.P., Hayden, M.R. (1993) Differential 3' polyadenylation of the Huntington disease gene results in two mRNA species with variable tissue expression. *Hum. Mol. Genet.* 2:1541-1545.
194. Lin, W.J., Gary, J.D., Yang, M.C., Clarke, S., Herschman, H.R. (1996) The mammalian immediate-early TIS21 protein and the leukemia-

- associated BTG1 protein interact with a protein-arginine N-methyltransferase. *J. Biol. Chem.* 271:15,034-15,044.
195. Lin, X., Sikink, R.A., Rusnak, F., Barber, D.L. (1999) Inhibition of calcineurin phosphatase activity by a calcineurin B homologous protein. *J. Biol. Chem.* 274:36,125-36,131.
196. Linnenbach, A.J., Seng, B.A., Wu, S., Robbins, S., Scollon, M., Pyrc, J.J., Druck, T., Huebner, K. (1993) Retroposition in a family of carcinoma-associated antigen genes. *Mol. Cell Biol.* 13:1507-1515.
197. Linstedt, A.D., Hauri, H.P. (1993) Giantin, a novel conserved Golgi membrane protein containing a cytoplasmic domain of at least 350 kDa. *Mol. Biol. Cell* 4:679-693.
198. Lipshutz, R.J., Fodor, S.P.A., Gingeras, T.R., Lockhart, D.J. (1999) High density synthetic oligonucleotide arrays. *Nature Genetics* 21:20-24.
199. Liu A.Y., Robinson R.R., Hellstrom K.E., Murray E.D. Jr., Chang C.P., Hellstrom I. (1987a) Chimeric mouse-human IgG1 antibody that can mediate lysis of cancer cells. *Proc. Natl. Acad. Sci.* 84:3439-3443.
200. Liu, A.Y., Robinson, R.R., Murray, E.D. Jr., Ledbetter, J.A., Hellstrom, I., Hellstrom, K.E. (1987b) Production of a mouse-human chimeric monoclonal antibody to CD20 with potent Fc-dependent biologic activity. *J. Immunol.* 139:3521-3526.
201. Lodish, H., Berk, A., Zipursky, S.L., Matsudaira, P., Baltimore, D., Darness, J. (1999) Molecular Cell Biology. 4th ed. WH Freeman & Co.
202. Loeffen, J.L., Triepels, R.H., van den Heuvel, L.P., Schuelke, M., Buskens, C.A., Smeets, R.J., Trijbels, J.M., Smeitink, J.A. (1998) cDNA of eight nuclear encoded subunits of NADH:ubiquinone oxidoreductase: human complex I cDNA characterization completed. *Biochem. Biophys. Res. Commun.* 253:415-422.
203. Los, M., Burek, C.J., Stroh, C., Benedyk, K., Hug, H., Mackiewicz. (2003) Anticancer drugs of tomorrow: apoptotic pathways as targets for drug design. *Drug Discov. Today* 15:67-77.
204. Lovering R, Trowsdale J. (1991) A gene encoding 22 highly related zinc fingers is expressed in lymphoid cell lines. *Nucleic Acids Res.* 19:2921-2928.

205. Luckow, V., Summers, M. (1988) Trends in the development of baculovirus expression vectors. *BioTechnology* 6:47-55.
206. MacBeath, G., Schreiber, S.L. (2000) Printing proteins as microarrays for high-throughput function determination. *Science* 289:1760-1763.
207. Machesky, L.M., Reeves, E., Wientjes, F., Mattheyse, F.J., Grogan, A., Totty, N.F., Burlingame, A.L., Hsuan, J.J., Segal, A.W. (1999) Mammalian actin-related protein 2/3 complex localizes to regions of lamellipodial protrusion and is composed of evolutionarily conserved proteins. *Biochem. J.* 328:105-112.
208. Machiels, J.P., van Baren, N., Marchand, M. (2002) Peptide-based cancer vaccines. *Semin. Oncol.* 29:494-502.
209. Mackay, A., Jones, C., Dexter, T., Silva, R.L., Bulmer, K., Jones, A., Simpson, P., Harris, R.A., Jat, P.S., Neville, A.M., Reis, L.F., Lakhani, S.R., O'Hare, M.J. (2003) cDNA microarray analysis of genes associated with ERBB2 (HER2/neu) overexpression in human mammary luminal epithelial cells. *Oncogene* 22:2680-2688.
210. Maeda, S., Kawai, T., Obinata, M., Fujiwara, H., Horiuchi, T., Saeki, Y., Sato, Y., Furusawa, M. (1985) Production of human alpha-interferon in silkworm using a baculovirus vector. *Nature* 315:592-594.
211. Mahajan, M.A., Murray, A., Samuels, H.H. (2002) NRC-interacting factor 1 is a novel cotransducer that interacts with and regulates the activity of the nuclear hormone receptor coactivator NRC. *Mol. Cell Biol.* 22:6883-6894.
212. Mahimkar, R.M., Baricos, W.H., Visaya, O., Pollock, A.S., Lovett, D.H. (2000) Identification, cellular distribution and potential function of the metalloprotease-disintegrin MDC9 in the kidney. *J. Am. Soc. Nephrol.* 11:595-603.
213. Mahnensmith, R.L., Aronson, P.S. (1985) Interrelationships among quinidine, amiloride, and lithium as inhibitors of the renal Na<sup>+</sup>-H<sup>+</sup> exchanger. *J. Biol. Chem.* 260:12,586-12,592.
214. Manning, G., Whyte, D.B., Martinez, R., Hunter, T., Sudarsanam, S. (2002) The protein kinase complement of the human genome. *Science* 298:1912-1934.

215. Marotti, K.R., Tomich, C.S. (1989) Simple and efficient oligonucleotide-directed mutagenesis using one primer and circular plasmid DNA template. (1989) *Gene Anal. Tech.* 6:67-70.
216. Martel-Pelletier, J., Welsch, D.J., and Pelletier, J.P. (2001) Metalloproteases and inhibitors in arthritic diseases. *Best Pract. Res. Clin. Rheumatol.* 15:805-829.
217. Martin, B.M., Tsuji, S., LaMarca, M.E., Maysak, K., Eliason, W., Ginns, E.I. (1988) Glycosylation and processing of high levels of active human glucocerebrosidase in invertebrate cells using a baculovirus expression vector. *DNA* 7:99-106.
218. Massari, M.E., Rivera, R.R., Volland, J.R., Quong, M.W., Breit, T.M., van Dongen, J.J., de Smit, O., Murre, C. (1998) Characterization of ABF-1, a novel basic helix-loop-helix transcription factor expressed in activated B lymphocytes. *Mol. Cell Biol.* 18:3130-3139.
219. Matz, M.V., Fradkov, A.F., Labas, Y.A., Savitsky, A.P., Zaraisky, A.G., Markelov, M.L., Lukyanov, S.A. (1999) Fluorescent proteins from nonbioluminescent *Anthozoa* species. *Nat. Biotechnol.* 17:969-973.
220. Mayer, B.J. (2001) SH3 domains: complexity in moderation. *J. Cell Sci.* 114:1253-1263.
221. Mayer, T.U., Kapoor, T.M., Haggarty, S.J., King, R.W., Schreiber, S.L., Mitchison, T.J. (1999) Small molecule inhibitor of mitotic spindle bipolarity identified in a phenotype-based screen. *Science* 286:971-974.
222. McGraw, R.A. III (1984) Dideoxy DNA sequencing with end-labeled oligonucleotide primers. *Anal. Biochem.* 143:298-303.
223. McKusick, V.A.. (2003) OMIM: Online Mendelian Inheritance in Man <http://www.ncbi.nlm.nih.gov/#104300>.
224. McPherson, M.J., Møller, S.G., Benyon, R., Howe, C. (2000) PCR Basics: From Background to Bench. Springer Verlag.
225. Merla, G., Ucla, C., Guipponi, M., Reymond, A. (2002) Identification of additional transcripts in the Williams-Beuren syndrome critical region. *Hum. Genet.* 110:429-438.
226. Miki, H., Setou, M., Kaneshiro, K., Hirokawa, N. (2001) All kinesin superfamily protein, KIF, genes in mouse and human. *Proc. Natl. Acad. Sci.* 98:7004-7011.



227. Milam, A.H., Rose, L., Cideciyan, A.V., Barakat, M.R., Tang, W.X., Gupta, N., Aleman, T.S., Wright, A.F., Stone, E.M., Sheffield, V.C., Jacobson, S.G. (2002) The nuclear receptor NR2E3 plays a role in human retinal photoreceptor differentiation and degeneration. *Proc. Natl. Acad. Sci.* 99:473-478.
228. Milligan, J.F., Matteucci, M.D., Martin, J.C. (1993) Current concepts in antisense drug design. *J. Med. Chem.* 36:1923-1937.
229. Mitch, W.E., Goldberg, A.L. (1996) Mechanisms of muscle wasting. The role of the ubiquitin-proteasome pathway. *N. Engl. J. Med.* 335:1897-1905.
230. Mitchell, D.A., Nair, S.K. (2000) RNA-transfected dendritic cells in cancer immunotherapy. *J. Clin. Invest.* 106:1065-1069.
231. Miyajima A. (2002) Functional analysis of yeast homologue gene associated with human DNA helicase causative syndromes. *Kokuritsu Iyakuhiin Shokuhin Eisei Kenkyusho Hokoku* 120:53-74.
232. Miyajima, A., Schreurs, J., Otsu, K., Kondo, A., Arai, K., Maeda, S. (1987) Use of the silkworm, *Bombyx mori*, and an insect baculovirus vector for high-level expression and secretion of biologically active mouse interleukin-3. *Gene* 58:273-281.
233. Monfardini, C., Schiavon, O., Caliceti, P., Morpurgo, M., Harris, J.M., Veronese, F.M. (1995) A branched monomethoxypoly(ethylene glycol) for protein modification. *Bioconjugate Chem.* 6:62-69.
234. Mori, N. (1997) Neuronal growth-associated proteins in neural plasticity and brain aging. *Nihon Shinkei Seishin Yakurigaku Zasshi* 17:159-167.
235. Mortlock, D.P., Nelson, M.R., Innis, J.W. (1996) An efficient method for isolating putative promoters and 5' transcribed sequences from large genomic clones. *Genome Res.* 6:327-335.
236. Murphy, D., Carter, D.A., eds. (1993) Transgenesis Techniques: Principles and Protocols. Humana Press.
237. Myers, E.W., Miller, W. (1988) Optimal alignments in linear space. *Comput. Appl. Biosci.* 4:11-7.
238. Nagata, K., Kawase, H., Handa, H., Yano, K., Yamasaki, M., Ishimi, Y., Okuda, A., Kikuchi, A., Matsumoto, K. (1995) Replication factor encoded

- by a putative oncogene, set, associated with myeloid leukemogenesis. *Proc. Natl. Acad. Sci.* 92:4279-4283.
239. Naora, H. (1999) Involvement of ribosomal proteins in regulating cell growth and apoptosis: translational modulation or recruitment for extraribosomal activity? *Immunol. Cell Biol.* 77:197-205.
240. Needleman, S.B., Wunch, C.D. (1970) A general method applicable to the search for similarities in the amino acid sequence of two proteins. *J. Mol. Biol.* 48:443-453.
241. Nelson, N., Harvey, W.R. (1999) Vacuolar and plasma membrane proton-adenosine triphosphatases. *Physiol. Rev.* 79:361-385.
242. Nishiyama, H., Higashitsuji, H., Yokoi, H., Itoh, K., Danno, S., Matsuda, T., Fujita, J. (1997) Cloning and characterization of human CIRP (cold-inducible RNA-binding protein) cDNA and chromosomal assignment of the gene. *Gene* 204:115-120.
243. Noma, T., Fujisawa, K., Yamashiro, Y., Shinohara, M., Nakazawa, A., Gondo, T., Ishihara, T., Yoshinobu, K. (2001) Structure and expression of human mitochondrial adenylate kinase targeted to the mitochondrial matrix. *Biochem. J.* 358:225-232.
244. Notredame, C., Higgins, D., Heringa, J. (2000) T-Coffee: A novel method for multiple sequence alignments. *J. Molec. Biol.* 302:205-217.
245. Okazaki, Y., Furuno, M., Kasukawa, T., Adachi, J., Bono, H., Kondo, S., Nikaido, I., Osato, N., Saito, R., Suzuki, H., Yamanaka, I., Kiyosawa, H., Yagi, K., Tomaru, Y., Hasegawa, Y., Nogami, A., Schonbach, C., Gojobori, T., Baldarelli, R., Hill, D.P., Bult, C., Hume, D.A., Quackenbush, J., Schriml, L.M., Kanapin, A., Matsuda, H., Batalov, S., Beisel, K.W., Blake, J.A., Bradt, D., Brusic, V., Chothia, C., Corbani, L.E., Cousins, S., Dalla, E., Dragani, T.A., Fletcher, C.F., Forrest, A., Frazer, K.S., Gaasterland, T., Gariboldi, M., Gissi, C., Godzik, A., Gough, J., Grimmond, S., Gustincich, S., Hirokawa, N., Jackson, I.J., Jarvis, E.D., Kanai, A., Kawaji, H., Kawasawa, Y., Kedziarski, R.M., King, B.L., Konagaya, A., Kurochkin, IV, Lee, Y., Lenhard, B., Lyons, P.A., Maglott, D.R., Maltais, L., Marchionni, L., McKenzie, L., Miki, H., Nagashima, T., Numata, K., Okido, T., Pavan, W.J., Pertea, G., Pesole, G., Petrovsky, N., Pillai, R., Pontius, J.U., Qi, D., Ramachandran, S., Ravasi, T., Reed, J.C., Reed, D.J., Reid, J., Ring, B.Z., Ringwald, M., Sandelin, A.,

- Schneider, C., Semple, C.A., Setou, M., Shimada, K., Sultana, R., Takenaka, Y., Taylor, M.S., Teasdale, R.D., Tomita, M., Verardo, R., Wagner, L., Wahlestedt, C., Wang, Y., Watanabe, Y., Wells, C., Wilming, L.G., Wynshaw-Boris, A., Yanagisawa, M., Yang, I., Yang, L., Yuan, Z., Zavolan, M., Zhu, Y., Zimmer, A., Carninci, P., Hayatsu, N., Hirozane-Kishikawa, T., Konno, H., Nakamura, M., Sakazume, N., Sato, K., Shiraki, T., Waki, K., Kawai, J., Aizawa, K., Arakawa, T., Fukuda, S., Hara, A., Hashizume, W., Imotani, K., Ishii, Y., Itoh, M., Kagawa, I., Miyazaki, A., Sakai, K., Sasaki, D., Shibata, K., Shinagawa, A., Yasunishi, A., Yoshino, M., Waterston, R., Lander, E.S., Rogers, J., Birney, E., Hayashizaki, Y.; FANTOM Consortium; RIKEN Genome Exploration Research Group Phase I & II Team. (2002) Analysis of the mouse transcriptome based on functional annotation of 60,770 full-length cDNAs. *Nature* 420:563-573.
246. Okayama, H., Berg, P. (1983) A cDNA cloning vector that permits expression of cDNA inserts in mammalian cells. *Mol. Cell. Biol.* 3:280-289.
247. Oksenberg, J.R., Barcellos, L.F., Hauser, S.L. (1999) Genetic aspects of multiple sclerosis. *Semin. Neurol.* 19:281-288.
248. Oliver, C.J., Shenolikar, S. (1998) Physiologic importance of protein phosphatase inhibitors. *Frontiers in Bioscience* 3:961-972.
249. O'Neil, N.J., Martin, R.L., Tomlinson, M.L., Jones, M.R., Coulson, A., Kuwabara, P.E. (2001) RNA-mediated interference as a tool for identifying drug targets. *Am. J. Pharmacogenomics* 1:45-53.
250. O'Neill, L.A. (2002) Signal transduction pathways activated by the IL-1 receptor/toll-like receptor superfamily. *Curr. Top. Microbiol. Immunol.* 270:47-61.
251. Page, D.C., Silber, S., Brown, L.G. (1999) Men with infertility caused by AZFc deletion can produce sons by intracytoplasmic sperm injection, but are likely to transmit the deletion and infertility. *Hum. Reprod.* 14:1722-1726.
252. Pan, C.X., Koeneman, K.S. (1999) A novel tumor-specific gene therapy for bladder cancer. *Med. Hypothesis* 53:130-135.
253. Pang, T., Wakabayashi, S., Shigekawa, M. (2001) Calcineurin homologous protein as an essential cofactor for Na<sup>+</sup>/H<sup>+</sup> exchangers. *J. Biol. Chem* 276:17,367-17,372.

254. Pang, T., Wakabayashi, S., Shigekawa, M. (2002) Expression of calcineurin B homologous protein 2 protects serum deprivation-induced cell death by serum-independent activation of Na<sup>+</sup>/H<sup>+</sup> exchanger. *J. Biol. Chem.* 277:43,771-43,777.
255. Papagerakis, S., Shabana, A.H., Depondt, J., Gehanno, P., Forest, N. (2003) Immunohistochemical localization of plakophilins (PKP1, PKP2, PKP3, and p0071) in primary oropharyngeal tumors: correlation with clinical parameters. *Hum. Pathol.* 34:565-572.
256. Pearson, W.R. (2000) Flexible sequence similarity searching with the FASTA3 program package. *Methods Mol. Biol.* 132:185-219.
257. Peattie, D.A., Harding, M.W., Fleming, M.A., DeCenzo, M.T., Lippke, J.A., Livingston, D.J., Benasutti, M. (1992) Expression and characterization of human FKBP52, an immunophilin that associates with the 90-kDa heat-shock protein and is a component of steroid receptor complexes. *Proc. Natl. Acad. Sci.* 89:10,974-10,978.
258. Peelle, B., Gururaja, T.L., Payan, D.G., Anderson, D.C. (2001) Characterization and use of green fluorescent proteins from *Renilla mulleri* and *Pharosarcus guernyi* for the human cell display of functional peptides. *J. Protein Chem.* 20:507-519.
259. Pepin, K., Momose, F., Ishida, N., Nagata, K. (2001) Molecular cloning of horse Hsp90 cDNA and its comparative analysis with other vertebrate Hsp90 sequences. *J. Vet. Med. Sci.* 63:115-124.
260. Perez Calvo, J.I., Inigo Gil, P., Giraldo Castellano, P., Torralba Cabeza, M.A., Civeira, F., Lario Garcia, S., Pocovi, M., Lara Garcia, S. (2000) Transforming growth factor beta (TGF-beta) in Gaucher's disease. Preliminary results in a group of patients and their carrier and non-carrier relatives. *Med. Clin. (Barc)* 115:601-604.
261. Perron, H., Garson, J.A., Bedin, F., Beseme, F., Paranhos-Baccala, G., Komurian-Pradel, F., Mallet, F., Tuke, P.W., Voisset, C., Blond, J.L., Lalande, B., Seigneurin, J.M., Mandrand, B., The Collaborative Research Group on Multiple Sclerosis (1997) Molecular identification of a novel retrovirus repeatedly isolated from patients with multiple sclerosis. *Proc. Natl. Acad. Sci.* 94:7583-7588.

262. Perry, A.C., Jones, R., Hall, L. (1995) Analysis of transcripts encoding novel members of the mammalian metalloprotease-like, disintegrin-like, cysteine-rich (MDC) protein family and their expression in reproductive and non-reproductive monkey tissues. *Biochem. J.* 312( Pt 1):239-244.
263. Pertl, U., Wodrich, H., Ruelmann, J.M., Gillies, S.D., Lode, H.N., Reisfeld, R.A. (2003) Immunotherapy with a posttranscriptionally modified DNA vaccine induces complete protection against metastatic neuroblastoma. *Blood* 101:649-654.
264. Pfützer, R.H., Whitcomb, D.C. (2001) SPINK1 mutations are associated with multiple phenotypes. *Pancreatology* 1:457-460.
265. Phillips, M.I., ed. (1999a) Antisense Technology. Part A. Methods in Enzymology Vol. 313. Academic Press, Inc.
266. Phillips, M.I., ed. (1999b) Antisense Technology. Part B. Methods in Enzymology Vol. 314. Academic Press, Inc.
267. Pietu, G., Alibert, O., Guichard, V., Lamy, B., Bois, F., Mariage-Sampson, R., Hougatte, R., Soularue, P., Auffray, C. (1996) Novel gene transcripts preferentially expressed in human muscles revealed by quantitative hybridization of a high density cDNA array. *Genome Res.* 6:492-503.
268. Pinkert, C.A., ed. (1994) Transgenic Animal Technology: A Laboratory Handbook. Academic Press.
269. Pisegna, J.R., Wank, S.A. (1996) Cloning and characterization of the signal transduction of four splice variants of the human pituitary adenylate cyclase activating polypeptide receptor. Evidence for dual coupling to adenylate cyclase and phospholipase C. *J. Biol. Chem.* 271:17,267-17,274.
270. Prentki, P., Krisch, H.M. (1984) *In vitro* insertional mutagenesis with a selectable DNA fragment. *Gene* 29:303-313.
271. Price, N.T., Hall, L., Proud, C.G. (1993) Cloning of cDNA for the beta-subunit of rabbit translation initiation factor-2 using PCR. *Biochim. Biophys. Acta* 1216:170-172.
272. Qin, J., Li, L. (2003) Molecular anatomy of the DNA damage and replication checkpoints. *Radiat. Res.* 159:139-148.
273. Racevskis, J., Dill, A., Stockert, R., Fineberg, S.A. (1996) Cloning of a novel nucleolar guanosine 5'-triphosphate binding protein autoantigen from a breast tumor. *Cell. Growth Differ.* 7:271-280.

274. Ramalho-Santos, M. (2002) "Stemness" *Science* 298:597-600.
275. Raval, P. (1994) Qualitative and quantitative determination of mRNA. *J. Pharmacol. Toxicol. Methods* 32:125-127.
276. Rebbe, N.F., Ware, J., Bertina, R.M., Modrich, P., Stafford, D.W. (1987) Nucleotide sequence of a cDNA for a member of the human 90-kDa heat-shock protein family. *Gene* 53:235-245.
277. Rechid, R., Vingron, M., Argos, P. (1989) A new interactive protein sequence alignment program and comparison of its results with widely used algorithms. *Comput. Appl. Biosci.* 5:107-113.
278. Rehli, M., Krause, S.W., Kreutz, M., Andreesen, R. (1995) Carboxypeptidase M is identical to the MAX.1 antigen and its expression is associated with monocyte to macrophage differentiation. *J. Biol. Chem.* 270:15644-15649.
279. Remington, J.P. (1985) Remington's Pharmaceutical Sciences. 17th ed. Mack Publishing Co.
280. Ribardo, D.A., Peterson, J.W., Chopra, A.K. (2002) Phospholipase A2-activating protein—an important regulatory molecule in modulating cyclooxygenase-2 and tumor necrosis factor production during inflammation. *Indian J. Exp. Biol.* 40:129-138.
281. Riley, J., Butler, R., Ogilvie, D., Finniear, R., Jenner, D., Powell, S., Anand, R., Smith, J.C., Markham, A.F. (1990) A novel, rapid method for the isolation of terminal sequences from yeast artificial chromosome (YAC) clones. *Nuc. Acids Res.* 18:2887-2890.
282. Ritter, R.C., Brenner, L.A., Tamura, C.S. (1994) Endogenous CCK and the peripheral neural substrates of intestinal satiety. *Ann. N. Y. Acad. Sci.* 713:255-267.
283. Robertson, H.M. (1996) Members of the pogo superfamily of DNA-mediated transposons in the human genome. *Mol. Gen. Genet.* 252:761-766.
284. Robertson, H.M., Zumpano, K.L. (1997) Molecular evolution of an ancient mariner transposon, Hsmar1, in the human genome. *Gene* 205:203-217.
285. Roepman, R., Bernoud-Hubac, N., Schick, D.E., Maugeri, A., Berger, W., Ropers, H.H., Cremers, F.P., Ferreira, P.A. (2000) The retinitis pigmentosa GTPase regulator (RPGR) interacts with novel transport-like

- proteins in the outer segments of rod photoreceptors. *Hum. Mol. Genet.* 9:2095-2105.
286. Roessler, B.J., Nosal, J.M., Smith, P.R., Heidler, S.A., Palella, T.D., Switzer, R.L., Becker, M.A. (1993) Human X-linked phosphoribosylpyrophosphate synthetase superactivity is associated with distinct point mutations in the PRPS1 gene. *J. Biol. Chem.* 268:26476-26481.
287. Roggenkamp, R., Janowicz, Z., Stanikowski, B., Hollenberg, C.P. (1984) Biosynthesis and regulation of the peroxisomal methanol oxidase from the methylotrophic yeast *Hansenula polymorpha*. *Mol. Gen. Genet.* 194:489-493.
288. Rosen, R.C., McKenna, K.E. (2002) PDE-5 inhibition and sexual response: pharmacological mechanisms and clinical outcomes. *Ann. Rev. Sex Res.* 13:36-88.
289. Rosato, R.R., Grant, S. (2003) Histone deacetylase inhibitors in cancer therapy. *Cancer Biol. Ther.* 2:30-37.
290. Rowland, J.M. (2002) Molecular genetic diagnosis of pediatric cancer: current and emerging methods. *Pediatr. Clin. North Am.* 49:1415-1435.
291. Saha, S., Bardelli, A., Buckhaults, P., Velculescu, V.E., Rago, C., St Croix, B., Romans, K.E., Choti, M.A., Lengauer, C., Kinzler, K.W., Vogelstein, B. (2001) A phosphatase associated with metastasis of colorectal cancer. *Science* 294:1343-1346.
292. Saiki, R.K., Gelfand, D.H., Stoffel, S., Scharf, S.J., Higuchi, R., Horn, G.T., Mullis, K.B., Erlich, H.A. (1988) Primer-directed enzymatic amplification of DNA with amplification of DNA with a thermostable DNA polymerase. *Science* 239:487-491.
293. Sambrook, J., Russell, D.W., Sambrook, J. (1989) Molecular Cloning, A Laboratory Manual. 2<sup>nd</sup> ed. Cold Spring Harbor Laboratory Press.
294. Sanchez, E.R., Faber, L.E., Henzel, W.J., Pratt, W.B. (1990) The 56-59-kilodalton protein identified in untransformed steroid receptor complexes is a unique protein that exists in cytosol in a complex with both the 70- and 90-kilodalton heat-shock proteins. *Biochemistry* 29:5145-5152.

295. Sayers, J.R., Krekel, C., Eckstein, F. (1992) Rapid high-efficiency site-directed mutagenesis by the phosphothioate approach. *Biotechniques* 13:592-596.
296. Schaeferling, M., Schiller, S., Paul, H., Kruschina, M., Pavlickova, M., Meerkamp, M., Giammasi, C., Kambhampati, D. (2002) Application of self-assembly techniques in the design of biocompatible protein microarray surfaces. *Electrophoresis* 23:3097-3105.
297. Schaffer, J.E., Lodish, H.F. (1994) Expression cloning and characterization of a novel adipocyte long chain fatty acid transport protein. *Cell* 79:393-395.
298. Schena, M., ed. (1999) DNA Microarrays: A Practical Approach. Oxford Univ. Press.
299. Schena, M., ed. (2000) Microarray Biochip Technology. 1st ed. Eaton Publishing Co.
300. Schlesinger, D.H. (1988a) MacRomolecular Sequencing and Synthesis: Selected Methods and Applications. Wiley-Liss.
301. Schlesinger, D.H., ed. (1988b) Current Methods in Sequence Comparison and Analysis. Macromolecule Sequencing and Synthesis. Selected Methods and Applications, pp. 127-149, Alan R. Liss, Inc.
302. Schonthal, A.H. (2001) Role of serine/threonine protein phosphatase 2A in cancer. *Cancer Lett.* 170:1-13.
303. Seelig, H.P., Schranz, P., Schroter, H., Wiemann, C., Renz, M. (1994) Macroglolin—a new 376 kD Golgi complex outer membrane protein as target of antibodies in patients with rheumatic diseases and HIV infections. *J. Autoimmun.* 7:67-91.
304. Selkoe, D.J. (2001) Presenilin, Notch, and the genesis and treatment of Alzheimer's disease. *Proc. Natl. Acad. Sci.* 98:11,039-11,041.
305. Setlow, J., Hollaender, A., eds. (1986) Genetic Engineering: Principles and Methods. Plenum Pub. Corp.
306. Shamay, M., Barak, O., Doitsh, G., Ben-Dor, I., Shaul, Y. (2002) Hepatitis B virus pX interacts with HBXAP, a PHD finger protein to coactivate transcription. *J. Biol. Chem.* 277:9982-9988.
307. Shao, H., Andres, D.A. (2000) A novel RalGEF-like protein, RGL3, as a candidate effector for rit and Ras. *J. Biol. Chem.* 275:26,914-26,924.



308. Sheppard, P., Kindsvogel, W., Xu, W., Henderson, K., Schlutsmeier, S., Whitmore, T.E., Kuestner, R., Garrigues, U., Birks, C., Roraback, J., Ostrander, C., Dong, D., Shin, J., Presnell, S., Fox, B., Haldeman, B., Cooper, E., Taft, D., Gilbert, T., Grant, F.J., Tackett, M., Krivan, W., McKnight, G., Clegg, C., Foster, D., Klucher, K.M. (2003) IL-28, IL-29 and their class II cytokine receptor IL-28R. *Nat. Immunol.* 4:63-68.
309. Shinnick, T.M., Sutcliffe, J.G., Green, N., Lerner, R.A. (1983) Synthetic peptide immunogens as vaccines. *Ann. Rev. Microbiol.* 37:425-446.
310. Shorter, J., Beard, M.B., Seemann, J., Dirac-Svejstrup, A.B., Warren, G. (2002) Sequential tethering of Golgins and catalysis of SNAREpin assembly by the vesicle-tethering protein p115. *J. Cell Biol.* 157:45-62.
311. Siebenlist, U., Simpson, R.B., Gilbert, W. (1980) *E. coli* RNA polymerase interacts homologously with two different promoters. *Cell* 20:269-281.
312. Siegal, G.J., Agranoff, B.W., Albers, R.W., Fisher, S.K., Uhler, M.D., eds. (1999) Basic Neurochemistry, Molecular, Cellular, and Medical Aspects. 6th ed. Lippencott, Williams & Wilkins.
313. Sladek, R., Bader, J.A., Giguere, V. (1997) The orphan nuclear receptor estrogen-related receptor alpha is a transcriptional regulator of the human medium-chain acyl coenzyme A dehydrogenase gene. *Mol. Cell Biol.* 17:5400-5409.
314. Slavin, S., Or, R., Aker, M., Shapira, M.Y., Panigrahi, S., Symeonidis, A., Cividalli, G., Nagler, A. (2001) Nonmyeloablative stem cell transplantation for the treatment of cancer and life-threatening nonmalignant disorders: past accomplishments and future goals. *Cancer Chemother. Pharmacol.* 48:S79-S84.
315. Smit, A.F., Riggs, A.D. (1996) Tiggers and DNA transposon fossils in the human genome. *Proc. Natl. Acad. Sci.* 93:1443-1448.
316. Smith, G.E., Ju, G., Ericson, B.L., Moschera, J., Lahm, H.W., Chizzonite, R., Summers, M.D. (1985) Modification and secretion of human interleukin 2 produced in insect cells by a baculovirus expression vector. *Proc. Natl. Acad. Sci.* 82:8404-8408.
317. Smith, T.F., Waterman, M.S. (1981) Comparison of biosequences. *Adv. Appl. Math.* 2:482-489.

318. Soares, M.B. (1997) Identification and cloning of differentially expressed genes. *Curr. Opin. Biotechnol.* 8:542-546.
319. Soejima, H., Kawamoto, S., Akai, J., Miyoshi, O., Arai, Y., Morohka, T., Matsuo, S., Niikawa, N., Kimura, A., Okubo, K., Mukai, T. (2001) Isolation of novel heart-specific genes using the BodyMap database. *Genomics.* 74:115-120.
320. Soulier, S., Vilotte, J.L., L'Huillier, P.J., Mercier, J.C. (1996) Developmental regulation of murine integrin beta 1 subunit- and Hsc73-encoding genes in mammary gland: sequence of a new mouse Hsc73 cDNA. *Gene* 172:285-289.
321. Southern, E., Mir, K., Shchepinov, M. (1999) Molecular interactions on microarrays. *Nature Genetics* 21:5-9.
322. Stein, C.A., Kreig, A.M., eds. (1998) Applied Antisense Oligonucleotide Technology. Wiley-Liss.
323. Steinhaur, C., Wingren, C., Hager, A.C., Borrebaeck, C.A. (2002) Single framework recombinant antibody fragments designed for protein chip applications. *Biotechniques, Supp.*:38-45.
324. Stetler-Stevenson, W.G., Liotta, L.A., Kleiner, D.E. Jr. (1993) Extracellular matrix 6: role of matrix metalloproteinases in tumor invasion and metastasis. *FASEB J.* 7:1434-1441.
325. Stewart, Z.A., Westfall, M.D., Pietenpol, J.A. (2003) Cell-cycle dysregulation and anticancer therapy. *Trends Pharmacol. Sci.* 24:139-145.
326. Stolz, L.E., Tuan, R.S. (1996) Hybridization of biotinylated oligo(dT) for eukaryotic mRNA quantitation. *Mol. Biotechnol.* 6:225-230.
327. Sturm, A., Dignass, A.U. (2002) Modulation of gastrointestinal wound repair and inflammation by phospholipids. *Biochim. Biophys. Acta* 1582:282-288.
328. Stutz, F., Bachi, A., Doerks, T., Braun, I.C., Seraphin, B., Wilm, M., Bork, P., Izaurralde, E. (2000) REF, an evolutionary conserved family of hnRNP-like proteins, interacts with TAP/Mex67p and participates in mRNA nuclear export. *RNA* 6:638-650.
329. Suh, Y.H., Checler, F. (2002) Amyloid precursor protein, presenilins, and alpha-synuclein: molecular pathogenesis and pharmacological applications in Alzheimer's disease. *Pharmacol. Rev.* 54:469-525.

330. Sutcliffe, J.G., Shinnick, T.M., Green, N., Lerner, R.A. (1983) Antibodies that react with predetermined sites on proteins. *Science* 219:660-666.
331. Tan, J., Town, T., Paris, D., Mori, T., Suo, Z., Crawford, F., Mattson, M.P., Flavell, R.A., Mullan, M. (1999) Microglial activation resulting from CD40-CD40L interaction after beta-amyloid stimulation. *Science* 286:2352-2355.
332. Tang, D.C., DeVit, M., Johnston, S.A. (1992) Genetic immunization is a simple method for eliciting an immune response. *Nature* 356:152-154.
333. Tekur, S., Pawlak, A., Guellaen, G., Hecht, N.B. (1999) Contrin, the human homologue of a germ-cell Y-box-binding protein: cloning, expression, and chromosomal localization. *J. Androl.* 20:135-144.
334. Terada, R., Yamamoto, K., Hakoda, T., Shimada, N., Okano, N., Baba, N., Ninomiya, Y., Gershwin, M.E., Shiratori, Y. (2003) Stromal cell-derived factor-1 from biliary epithelial cells recruits CXCR4-positive cells: implications for inflammatory liver diseases. *Lab. Invest.* 83:665-672.
335. Thompson, J.D., Higgins, D.G., Gibbon, T.J. (1994) CLUSTAL W: improving the sensitivity of progressive multiple sequence alignment through sequence weighting, position-specific gap penalties and weight matrix choice. *Nucleic Acids Res.* 22:4673-80.
336. Tilburn, J., Scazzocchio, C., Taylor, G.G., Zabicky-Zissman, J.H., Lockington, R.A., Davies, R.W. (1983) Transformation by integration in *Aspergillus nidulans*. *Gene* 26:205-221.
337. Trounson, A. (2002) Human embryonic stem cells: mother of all cell and tissue types. *Reprod. Biomed. Online* 4 Suppl. 1:58-63.
338. Tsuda, T., Gallup, M., Jany, B., Gum, J., Kim, Y., Basbaum, C. (1993) Characterization of a rat airway cDNA encoding a mucin-like protein. *Biochem. Biophys. Res. Commun.* 195:363-373.
339. Tukey, R.H., Pendurthi, U.R., Nguyen, N.T., Green, M.D., Tephly, T.R. (1993) Cloning and characterization of rabbit liver UDP-glucuronosyltransferase cDNAs. Developmental and inducible expression of 4-hydroxybiphenyl UGT2B13. *J. Biol. Chem.* 268:15,260-15,266.

340. Vainberg, I.E., Lewis, S.A., Rommelaere, H., Ampe, C., Vandekerckhove, J., Klein, H.L., Cowan, N.J. (1998) Prefoldin, a chaperone that delivers unfolded proteins to cytosolic chaperonin. *Cell* 93:863-873.
341. Vale, R.D. (2003) The molecular motor toolbox for intracellular transport. *Cell* 112:467-480.
342. Vallejo, M., Ron, D., Miller, C.P., Habener, J.F. (1993) C/ATF, a member of the activating transcription factor family of DNA-binding proteins, dimerizes with CAAT/enhancer-binding proteins and directs their binding to cAMP response elements. *Proc. Natl. Acad. Sci.* 90:4679-4683.
343. van den Berg, J.A., van der Laken, K.J., van Ooyen, A.J., Renniers, T.C., Rietveld, K., Schaap, A., Brake, A.J., Bishop, R.J., Schultz, K., Moyer, D. (1990) *Kluyveromyces* as a host for heterologous gene expression: expression and secretion of prochymosin. *Bio/Technology* 8:135-139.
344. Van den Berghe, L., Laurell, H., Huez, I., Zanibellato, C., Prats, H., Bugler, B. (2000) FIF [fibroblast growth factor-2 (FGF-2)-interacting-factor], a nuclear putatively antiapoptotic factor, interacts specifically with FGF-2. *Mol. Endocrinol.* 14:1709-1724.
345. Van Den Blink, B., Ten Hove T., Van Den Brink G.R., Peppelenbosch M.P., Van Deventer S.J. (2002) From extracellular to intracellular targets, inhibiting MAP kinases in treatment of Crohn's disease. *Ann. N. Y. Acad. Sci.* 973:349-58.
346. van der Spoel, A.C., Jeyakumar, M., Butters, T.D., Charlton, H.M., Moore, H.D., Dwck, R.A., Platt, F.M. (2002) Reversible infertility in male mice after oral administration of alkylated imino sugars: a nonhormonal approach to male contraception. *Proc. Natl. Acad. Sci.* 99:17173-17178.
347. Van Eerdewegh, P., Little, R.D., Dupuis, J., Del Mastro, R.G., Falls, K., Simon, J., Torrey, D., Pandit, S., McKenny, J., Braunschweiger, K., Walsh, A., Liu, Z., Hayward, B., Folz, C., Manning, S.P., Bawa, A., Saracino, L., Thackston, M., Benckekroun, Y., Capparell, N., Wang, M., Adair, R., Feng, Y., Dubois, J., FitzGerald, M.G., Huang, H., Gibson, R., Allen, K.M., Pedan, A., Danzig, M.R., Umland, S.P., Egan, R.W., Cuss, F.M., Rorke, S., Clough, J.B., Holloway, J.W., Holgate, S.T., Keith, T.P. (2002) Association of the ADAM33 gene with asthma and bronchial hyperresponsiveness. *Nature.* 418:426-430.

348. Van Laar, J.M., Tyndall, A. (2003) Intense immunosuppression and stem-cell transplantation for patients with severe rheumatic autoimmune disease: a review. *Cancer Control* 10:57-65.
349. Verhey, K.J., Meyer, D., Deehan, R., Blenis, J., Schnapp, B.J., Rapoport, T.A., Margolis, B. (2001) Cargo of kinesin identified as JIP scaffolding proteins and associated signaling molecules. *J. Cell Biol.* 152:959-970.
350. Vlak, J.M., Klinkenberg, F.A., Zaai, K.J., Usmany, M., Klinge -Roode, E.C., Geervliet, J.B., Roosien, J., van Lent, J.W. (1988) Functional studies on the p10 gene of Autographa californica nuclear polyhedrosis virus using a recombinant expressing a p10-beta- galactosidase fusion gene. *J. Gen. Virol.* 69:765-776.
351. Voisset, C., Bouton, O., Bedin, F., Düret, L., Mandrand, B., Mallet, F., Paranhos-Baccala, G. (2000) Chromosomal distribution and coding capacity of the human endogenous retrovirus HERV-W family. *AIDS Res. Hum. Retroviruses* 16:731-740.
352. Wagner, R.W., Matteucci, M.D., Lewis, J.G., Gutierrez, A.J., Moulds, C., Froehler, B.C. (1993) Antisense gene inhibition by oligonucleotides containing C-5 propyne pyrimidines. *Science* 260:1510-1513.
353. Wagner, R.W., Matteucci, M.D., Grant, D., Huang, T., Froehler, B.C. (1996) Potent and selective inhibition of gene expression by an antisense heptanucleotide. *Nat. Biotechnol.* 14:840-844.
354. Walker, J.E., Arizmendi, J.M., Dupuis, A., Fearnley, I.M., Finel, M., Medd, S.M., Pilkington, S.J., Runswick, M.J., Skehel, J.M. (1992) Sequences of 20 subunits of NADH:ubiquinone oxidoreductase from bovine heart mitochondria. Application of a novel strategy for sequencing proteins using the polymerase chain reaction. *J. Mol. Biol.* 226:1051-1072.
355. Walsh, A.C., Feulner, J.A., Reilly, A. (2001) Evidence for functionally significant polymorphism of human glutamate cysteine ligase catalytic subunit: association with glutathione levels and drug resistance in the National Cancer Institute tumor cell line panel. *Toxicol. Sci.* 61:218-223.
356. Wang, J., Kirby, C.E., Herbst, R. (2002) The tyrosine phosphatase PRL-1 localizes to the endoplasmic reticulum and the mitotic spindle and is required for normal mitosis. *J. Biol. Chem.* 277:46659-46668.

357. Wang, M.S., Schinzel, A., Kotzot, D., Balmer, D., Casey, R., Chodirker, B.N., Gyftodimou, J., Petersen, M.B., Lopez-Rangel, E., Robinson, W.P. (1999) Molecular and clinical correlation study of Williams-Beuren syndrome: No evidence of molecular factors in the deletion region or imprinting affecting clinical outcome. *Am. J. Med. Genet.* 86:34-43.
358. Wax, S.D., Rosenfield, C.L., Taubman, M.B. (1994) Identification of a novel growth factor-responsive gene in vascular smooth muscle cells. *J. Biol. Chem.* 269:13,041-13,047.
359. Wei, S., Charmley, P., Concannon, P. (1997) Organization, polymorphism, and expression of the human T-cell receptor AV1 subfamily. *Immunogenetics* 45:405-412.
360. Weishaar, R.E., Cain, M.H., Bristol, J.A. (1985) A new generation of phosphodiesterase inhibitors: multiple molecular forms of phosphodiesterase and the potential for drug selectivity. *J. Med. Chem.* 28:537-545.
361. Weiner, H.L., Selkoe, D.J. (2002) Inflammation and therapeutic vaccination in CNS diseases. *Nature* 420:879-884.
362. Weiner, M.P., Felts, K.A., Simcox, T.G., Braman, J.C. (1993) A method for the site-directed mono- and multi- mutagenesis of double-stranded DNA. *Gene* 126:35-41.
363. Weinstein, M.E., Grossman, A., Perle, M.A., Wilmot, P.L., Verma, R.S., Silver, R.T., Arlin, Z., Allen, S.L., Amorosi, E., Waintraub, S.E., et al. (1988) The karyotype of Philadelphia chromosome-negative, bcr rearrangement-positive chronic myeloid leukemia. *Cancer Genet Cytogenet.* 35:223-229.
364. Weissman, I.L. (2000) Translating stem and progenitor cell biology to the clinic: barriers and opportunities. *Science* 287:1442-1446.
365. Weng, S., Gu, K., Hammond, P.W., Lohse, P., Rise, C., Wagner, R.W., Wright, M.C., Kuimelis, R.G. (2002) Generating addressable protein microarrays with PROfusion covalent mRNA-protein fusion technology. *Proteomics* 2:48-57.
366. Wenger, R.H., Rochelle, J.M., Seldin, M.F., Kohler, G., Nielsen, P.J. (1993) The heat stable antigen (mouse CD24) gene is differentially regulated but has a housekeeping promoter. *J. Biol. Chem.* 268:23,345-23,352.

367. Werner, T., Brack-Werner, R., Leib-Mosch, C., Backhaus, H., Erfle, V., Hehlmann, R. (1990) S71 is a phylogenetically distinct endogenous retroviral element with structural and sequence homology to mimian sarcoma virus (SSV). *Virology* 174:225-238.
368. Wick, G., Kromer, G., Neu, N., Fassler, R., Ziemiecki, A., Muller, R.G., Ginzel, M., Beladi, I., Kuhr, T., Hala, K. (1987) The multi-factorial pathogenesis of autoimmune disease. *Immunol. Lett.* 16:249-257.
369. Wieczorek, H., Brown, D., Grinstein, S., Ehrenfeld, J., Harvey, W.R. (1999) Animal plasma membrane energization by proton-motive V-ATPases. *Bioessays* 21:637-648.
370. Wieser, R. (2002) Rearrangements of chromosomal band 3q21 in myeloid leukemia. *Leuk. Lymphoma* 43:59-65.
371. Winssinger, N., Ficarro, S., Schultz, P.G., and Harris, J.L. (2002) Profiling protein function with small molecule microarrays. *Proc. Natl. Acad. Sci.* 99:11,139-11,144.
372. Wojtowicz-Praga, S. (1999) Clinical potential of matrix metalloprotease inhibitors. *Drugs R. D.* 1:117-129.
373. Wu, A.M., Gallo, R.C. (1975) Reverse Transcriptase. *CRC Crit. Rev. Biochem.* 3:289-347.
374. Xu, C.W., Mendelsohn, A.R., Brent, R. (1997) Cells that register logical relationships among proteins. *Proc. Natl. Acad. Sci. (USA)* 94:12,473-12,478.
375. Xu, Y., Piston, D.W., Johnson, C.H. (1999) A bioluminescence resonance energy transfer (BRET) system: Application to interacting circadian clock proteins. *Proc. Natl. Acad. Sci.* 96:151-156.
376. Yang, N., Shigeta, H., Shi, H., Teng, C.T. (1996) Estrogen-related receptor, hERR1, modulates estrogen receptor-mediated response of human lactoferrin gene promoter. *J. Biol. Chem.* 271:5795-5804.
377. Yelton, M.M., Hamer, J.E., Timberlake, W.E. (1984) Transformation of *Aspergillus nidulans* by using a trpC plasmid. *Proc. Natl. Acad. Sci.* 81:1470-1474.
378. Yoshihama, M., Uechi, T., Asakawa, S., Kawasaki, K., Kato, S., Higa, S., Maeda N., Minoshima, S., Tanaka, T., Shimizu, N., Kenmochi, N. (2002)

- The human ribosomal protein genes: sequencing and comparative analysis of 73 genes. *Genome Res.* 12:379-390.
379. Yu, L., Zhang, Z., Loewenstein, P.M., Desai, K., Tang, Q., Mao, D., Symington, J.S., Green, M. (1995) Molecular cloning and characterization of a cellular protein that interacts with the human immunodeficiency virus type 1 Tat transactivator and encodes a strong transcriptional activation domain. *J. Virol.* 69:3007-3016.
380. Yu, Z., Restifo, N.P. (2002) Cancer vaccines: progress reveals new complexities. *J. Clin. Invest.* 110:289-294.
381. Zallipsky, S. (1995) Functionalized poly(ethylene glycols) for preparation of biologically relevant conjugates. *Bioconjugate Chem.*, 6:150-165.
382. Zhang, Q., Acland, G.M., Wu, W.X., Johnson, J.L., Pearce-Kelling, S., Tulloch, B., Vervoort, R., Wright, A.F., Aguirre, G.D. (2002) Different RPGR exon ORF15 mutations in Canids provide insights into photoreceptor cell degeneration. *Hum. Mol. Genet.* 11:993-1003.
383. Zhang, W.M., Popova, S.N., Bergman, C., Velling, T., Gullberg, M.K., Gullberg, D. (2002) Analysis of the human integrin alpha11 gene (ITGA11) and its promoter. *Matrix Biol.* 21:513-523.
384. Zhao, H., Grabowski, G.A. (2002) Gaucher disease: Perspectives on a prototype lysosomal disease. *Cell Mol. Life Sci.* 59:694-707.
385. Zhao, N., Hashida, H., Takhshi, N., Misumi, Y., Sakaki, Y. (1995) High-density cDNA filter analysis: a novel approach for large-scale quantitative analysis of gene expression. *Gene* 156:207-215.
386. Zhao, Y., Hong, D.H., Pawlyk, B., Yue, G., Adamian, M., Grynberg, M., Godzik, A., Li, T. (2003) The retinitis pigmentosa GTPase regulator (RPGR)-interacting protein: Subserving RPGR function and participating in disk morphogenesis. *Proc. Natl. Acad. Sci.* 100:3965-3970
387. Zhu, D.L. (1989) Oligonucleotide-directed cleavage and repair of a single stranded vector: a method of site-specific mutagenesis. *Anal. Biochem.* 177:120-124.
388. Zhu, H., Bilgin, M., Bangham, R., Hall, D., Casamayor, P., Bertone, P., Lan, N., Jansen, R., Bidlingmaier, S., Houfek, T., Mitchell, T., Miller, P.,



- Dean, R.A., Gerstein, M., Snyder, M. (2001) Global analysis of protein activities using proteome chips. *Science* 293:2101-2105.
389. Zhu, H., Klemic, J.F., Chang, S., Bertone, P., Casamayor, A., Klemic, K.G., Smith, D., Gerstein, M., Reed, M.A., Snyder, M. (2000) Analysis of yeast protein kinases using protein chips. *Nat. Genetics* 26:283-289.
390. Zhu, H., Snyder, M. (2003) Protein chip technology. *Curr. Opin. Chem. Biol.* 7:55-63.
391. Zhu, J., Kahn, C.R. (1997) Analysis of a peptide hormone-receptor interaction in the yeast two-hybrid system *Proc. Natl. Acad. Sci.* 94:13,063-13,068.

WO 2005/005597

PCT/US2003/027106

**SEQUENCE LISTING**

[0627] A sequence listing transmittal sheet and a sequence listing in paper format accompanies this application.

# CLAIMS

1. A first nucleic acid molecule comprising a polynucleotide sequence chosen from at least one polynucleotide sequence according to SEQ ID NOS.: 1-104.
2. The nucleic acid molecule of claim 1, wherein the nucleic acid molecule is a DNA or a RNA molecule.
3. An animal injected with the nucleic acid molecule of claim 1.
4. A double-stranded isolated nucleic acid molecule comprising the first nucleic acid molecule of claim 1 and its complement.
5. The nucleic acid molecule of claim 4, wherein the first polynucleotide sequence encodes a polypeptide chosen from a polypeptide comprising a signal peptide, a mature polypeptide that lacks a signal peptide, a signal peptide, a biologically active fragment of a polypeptide, a polypeptide lacking a signal peptide cleavage site, a polypeptide consisting essentially of a N-terminal fragment that contains a Pfam domain, and a polypeptide consisting essentially of a C-terminal fragment that contains a Pfam domain.
6. A second nucleic acid molecule comprising a second polynucleotide sequence that is at least about 70%, or about 80%, or about 90%, or about 95% homologous to the first nucleic acid molecule of claim 1.
7. A second isolated nucleic acid molecule comprising a second polynucleotide sequence that hybridizes to the first polynucleotide sequence of claim 1 under high stringency conditions.
8. The second isolated nucleic acid molecule of claim 6, wherein the second polynucleotide sequence is complementary to the first polynucleotide sequence.
9. A vector comprising the nucleic acid molecule of claim 1 and a promoter that drives the expression of the nucleic acid molecule.
10. The vector of claim 9, wherein the promoter is chosen from one or more of a promoter that is naturally contiguous to the nucleic acid molecule, a promoter that is not naturally contiguous to the nucleic acid molecule, an inducible promoter, a conditionally active promoter, a constitutive promoter, and a tissue specific promoter.
11. A host cell transformed, transfected, transduced, or infected with the nucleic acid molecule of claim 1.

12. The host cell of claim 11, wherein the cell is chosen from one or more of a prokaryotic cell, a eucaryotic cell, a human cell, a mammalian cell, an insect cell, a fish cell, a plant cell, and a fungal cell.

13. A nucleic acid composition comprising a pharmaceutically acceptable carrier or a buffer and one or more compositions chosen from the nucleic acid molecule of claim 1, the nucleic acid molecule of claim 4, the vector of claim 9, and the host cell of claim 11.

14. One or more polypeptide molecules comprising a polypeptide sequence chosen from at least one amino acid sequence encoded by SEQ ID NOS.: 1-104.

15. An animal injected with the polypeptide molecule of claim 14.

16. The polypeptide of claim 14, wherein the polypeptide has a function chosen from an agonist, an antagonist, a ligand, and a receptor.

17. The polypeptide of claim 14, wherein the polypeptide is chosen from a polypeptide comprising a signal peptide, a mature polypeptide that lacks a signal peptide, a signal peptide, a biologically active fragment of a polypeptide, a polypeptide lacking a signal peptide cleavage site, a biologically active fragment consisting essentially of an N-terminal fragment containing a Pfam domain, and a C-terminal fragment containing a Pfam domain.

18. A polypeptide composition comprising the polypeptide molecule of claim 14 and a pharmaceutically acceptable carrier or a buffer.

19. A cell culture medium comprising the polypeptide of claim 14.

20. The cell culture medium of claim 19, further comprising responder cells chosen from one or more T cells, B cells, NK cells, dendritic cells, macrophages, muscle cells, stem cells, epithelial skin cells, fat cells, blood cells, brain cells, bone marrow cells, endothelial cells, retinal cells, bone cells, kidney cells, pancreatic cells, liver cells, spleen cells, prostate cells, cervical cells, ovarian cells, breast cells, lung cells, liver cells, soft tissue cells, colorectal cells, cells of the gastrointestinal tract, and cancer cells.

21. The cell culture medium of claim 20, wherein the responder cells proliferate in the medium.

22. The cell culture medium of claim 20, wherein the responder cells are inhibited in the medium.

23. A cell culture comprising transfected cells, wherein the transfected cells are transfected with the polynucleotide of claim 1.
24. The cell culture of claim 23, further comprising responder cells chosen from one or more T cells, B cells, NK cells, dendritic cells, macrophages, muscle cells, stem cells, epithelial skin cells, fat cells, blood cells, brain cells, bone marrow cells, endothelial cells, retinal cells, bone cells, kidney cells, pancreatic cells, liver cells, spleen cells, prostate cells, cervical cells, ovarian cells, breast cells, lung cells, liver cells, soft tissue cells, colorectal cells, cells of the gastrointestinal tract, and cancer cells.
25. The cell culture of claim 23, wherein the responder cells proliferate in the cell culture.
26. The cell culture of claim 23, wherein the responder cells are inhibited in the cell culture.
27. A method of making a transformed, transfected, transduced, or infected host cell comprising:
  - (a) providing a composition comprising the vector of claim 9, and
  - (b) allowing a host cell to come into contact with the vector to form a transformed, transfected, transduced, or infected host cell.
28. A method of making a polypeptide comprising:
  - (a) providing a nucleic acid molecule that comprises a polynucleotide sequence encoding the polypeptide of claim 14;
  - (b) introducing the nucleic acid molecule into an expression system; and
  - (c) allowing the polypeptide to be produced.
29. A method of making a polypeptide comprising:
  - (a) providing a composition comprising the host cell of claim 11;
  - (b) culturing the host cell to produce the polypeptide; and
  - (c) allowing the polypeptide to be produced.
30. A diagnostic kit comprising a polynucleotide molecule, wherein the polynucleotide molecule comprises a sequence chosen from (a) at least 6, (b) at least 7, (c) at least 8, and (d) at least 9 contiguous nucleotides chosen from the nucleic acid molecule of claim 1.

31. A diagnostic kit comprising a polypeptide molecule, wherein the polypeptide molecule comprises an amino acid sequence or a biologically active fragment thereof, derived from the nucleic acid molecule of claim 1.
32. A genetically modified mouse comprising a deletion, substitution, or modification of a sequence chosen from SEQ ID NOS.: 1-104, wherein the deletion, substitution or modification prevents or reduces expression of said sequence and results in a mouse deficient in or completely lacking one or more gene products of a sequence chosen from SEQ ID NOS.: 1-104.
33. A method of determining the presence of the nucleic acid molecule of claim 1 or its complement comprising:
  - (a) providing a complement to the nucleic acid molecule or providing a complement to the complement of the nucleic acid molecule;
  - (b) allowing the molecules to interact; and
  - (c) determining whether interaction has occurred.
34. A method of determining the presence of an antibody to the polypeptide of claim 14 in a sample, comprising:
  - (a) providing the polypeptide;
  - (b) allowing the polypeptide to interact with any specific antibody in the sample; and
  - (c) determining whether interaction has occurred.
35. An antibody specifically recognizing, binding to, and/or modulating the biological activity of at least one polypeptide encoded by a nucleic acid molecule of claim 1, or a biologically active fragment thereof.
36. An antibody composition comprising the antibody of claim 35 and a pharmaceutically acceptable carrier.
37. The antibody of claim 35, wherein the antibody is chosen from one or more of a monoclonal antibody, a polyclonal antibody, a single chain antibody, an antibody comprising a backbone of a molecule with an Ig domain, a targeting antibody, a neutralizing antibody, a stabilizing antibody, an enhancing antibody, an antibody agonist, an antibody antagonist, an antibody that promotes endocytosis of a target antigen, a cytotoxic antibody, an antibody that mediates ADCC, a human antibody, a non-human primate antibody, a non-primate animal antibody, a rabbit antibody, a mouse antibody, a rat antibody, a sheep antibody, a goat antibody, a horse

antibody, a porcine antibody, a cow antibody, a chicken antibody, a humanized antibody, a primatized antibody, and a chimeric antibody.

38. The antibody of claim 37, wherein the antibody is produced in a manner chosen from *in vivo* and *in vitro*.

39. The antibody of claim 37, wherein the antibody is produced in an organism chosen from a prokaryote and a eukaryote.

40. The antibody of claim 39, wherein the organism is chosen from a bacterial cell, a fungal cell, a plant cell, an insect cell, and a mammalian cell.

41. The antibody of claim 40, wherein the cell is chosen from a yeast cell, an *Aspergillus* cell, an SF9 cell, a High Five cell, a cereal plant cell, a tobacco cell, and a tomato cell.

42. The cytotoxic antibody of claim 37, further comprising one or more cytotoxic component chosen from a radioisotope, a microbial toxin, a plant toxin, and a chemical compound.

43. The cytotoxic antibody of claim 42, wherein the chemical compound is chosen from doxorubicin and cisplatin.

44. The antibody of claim 35, wherein the antibody has a function chosen from specifically inhibiting the binding of the polypeptide to a ligand, specifically inhibiting the binding of the polypeptide to a substrate, specifically inhibiting the binding of the polypeptide as a ligand, and specifically inhibiting the binding of the polypeptide as a substrate.

45. A bacteriophage, wherein the antibody of claim 35, or a fragment thereof, is displayed on the bacteriophage.

46. A bacterial cell comprising the bacteriophage of claim 45.

47. A non-human animal injected with the antibody composition of claim 36.

48. A host cell that secretes the antibody of claim 35.

49. A method of making an antibody, comprising:

(a) introducing a polypeptide, polynucleotide encoding the polypeptide, or a biologically active fragment thereof into an animal in sufficient amount to elicit generation of antibodies specific to the polypeptide, wherein the polypeptide:

(i) is encoded by the nucleic acid molecule of claim 1; or

(ii) comprises the polypeptide sequence of claim 14; and

(b) recovering the antibodies therefrom.

50. The method of claim 49, further comprising after step (a), the step of isolating a spleen from the animal injected with the polypeptide or polynucleotide or a fragment thereof, and the step of recovering the antibodies from the spleen cells.

51. The method of claim 50, further comprising the step of making a hybridoma using cells from the spleen and selecting a hybridoma that secretes the antibodies.

52. The method of claim 50, further comprising making a polynucleotide library from the spleen cells, selecting a cDNA clone that produces the antibodies, and expressing the cDNA clone in an expression system to produce antibodies or fragments thereof.

53. A method of modulating biological activity comprising:

(a) providing the antibody of claim 35; and

(b) contacting the antibody with a first human or a non-human host cell thereby modulating the activity of a first human or non-human animal host cell, or a second host cell.

54. The method of claim 53, wherein the modulation of biological activity is chosen from enhancing cell activity directly, enhancing cell activity indirectly, inhibiting cell activity directly, and inhibiting cell activity indirectly.

55. The method of claim 53, wherein the step of contacting the antibody with a first human or non-human host cells results in recruitment of the second host cell.

56. The method of claim 53, wherein the first host cell is a cancer cell.

57. The method of claim 53, wherein the first or second host cell is chosen from a T cell, B cell, NK cell, dendritic cell, macrophage, muscle cell, stem cell, skin cell, fat cell, blood cell, brain cell, bone marrow cell, endothelial cell, retinal cell, bone cell, kidney cell, pancreatic cell, liver cell, spleen cell, prostate cell, cervical cell, ovarian cell, breast cell, lung cell, liver cell, soft tissue cell, colorectal cell, and gastrointestinal tract cell.

58. A method of diagnosing a disease, disorder, syndrome, or condition chosen from cancer, proliferative, inflammatory, immune, metabolic, genetic, bacterial, and viral diseases, disorders, syndromes, or conditions in a patient, comprising:

(a) providing the antibody of claim 35;



- (b) allowing the antibody to contact a patient sample; and
  - (c) detecting specific binding between the antibody and an antigen in the sample to determine whether the subject has cancer, a proliferative, inflammatory, immune, metabolic, genetic, bacterial, or viral disease, disorder, syndrome, or condition.
59. A method of diagnosing a disease, disorder, syndrome, or condition chosen from cancer, proliferative, inflammatory, immune, bacterial, and viral diseases, disorders, syndromes, or conditions in a patient, comprising:
- (a) providing a polypeptide that specifically binds the antibody of claim 35;
  - (b) allowing the polypeptide to contact a patient sample; and
  - (c) detecting specific binding between the polypeptide and any interacting molecule in the sample to determine whether the subject has cancer, a proliferative, inflammatory, immune, bacterial, or viral disease, disorder, syndrome, or condition.
60. A method of identifying an agent that modulates the biological activity of a polypeptide comprising:
- (a) providing a polypeptide or an active fragment thereof, wherein the polypeptide comprises at least one amino acid sequence encoded by SEQ ID NOS.: 1-104;
  - (b) allowing at least one agent to contact the polypeptide; and
  - (c) selecting an agent that binds the polypeptide or affects the biological activity of the polypeptide.
61. The method of claim 60, wherein the polypeptide is expressed on a cell surface.
62. A modulator composition comprising a modulator and a pharmaceutically acceptable carrier, wherein the modulator is obtainable by the method of claim 60.
63. The modulator composition of claim 62, wherein the modulator is an antibody.
64. A method of treating a disease, disorder, syndrome, or condition in a subject, comprising administering the composition of any one of claims 13, 18, and 36 to the subject.

65. The method of claim 64, wherein the composition is administered in a manner chosen from orally, parenterally, by implantation, by inhalation, intranasally, intravenously, intra-arterially, intracardiacally, subcutaneously, intraperitoneally, transdermally, intraventricularly, intracranially, and intrathecally.

66. The method of claim 64, wherein the disease, disorder, syndrome, or condition is chosen from cancer, a proliferative, inflammatory, immune, metabolic, genetic, bacterial, and viral disease, disorder, syndrome, or condition.

67. The method of claim 64, wherein the disease is cancer.

68. A method of treating a disease, disorder, syndrome, or condition chosen from cancer, proliferative, inflammatory, immune, metabolic, genetic, bacterial, and viral diseases, disorders, syndromes, or conditions in a subject, comprising:

(a) providing an antibody composition that comprises a first antibody or fragment thereof that specifically binds to a first epitope of a first polypeptide or a biologically active fragment thereof, wherein the first polypeptide:

- (i) is encoded by the nucleic acid molecule of claim 1; or
- (ii) comprises the polypeptide of claim 14; and

(b) administering the antibody composition to the subject.

69. The method of claim 68, wherein the antibody composition further comprises a second antibody that binds specifically to or interferes with the activity of a second epitope of the first polypeptide or to a first epitope of a second polypeptide.

70. The method of claim 69, wherein the second polypeptide comprises the polypeptide of 14.

71. A kit comprising the antibody of claim 35 and instructions for its use.

72. A method of gene therapy, comprising:

(a) providing a polynucleotide comprising a nucleic acid molecule encoding the antibody of claim 35; and

(b) administering the polynucleotide to a subject.

73. A method for prophylactic or therapeutic treatment of a subject, comprising:

- (a) providing a vaccine; and
- (b) administering the vaccine to the subject;

wherein the vaccine comprises a polynucleotide or a polypeptide chosen from at least one sequence according to SEQ ID NOS.: 1-104 or a biologically active fragment thereof.

74. The method of claim 73, wherein the vaccine is a cancer vaccine, and the polypeptide is a cancer antigen.

75. A method of inhibiting transcription or translation of a first polynucleotide encoding a first polypeptide, comprising:

(a) providing a second polynucleotide that hybridizes to the first polynucleotide, wherein the first polynucleotide comprises a polynucleotide sequence chosen from:

- (i) at least one polynucleotide sequence according to SEQ ID NOS.: 1-104;
  - (ii) a polynucleotide encoding a polypeptide comprising an amino acid sequence chosen from at least one amino acid sequence according to SEQ ID NOS.: 1-104; and
  - (iii) a polynucleotide encoding a fragment of a polypeptide comprising an amino acid sequence chosen from at least one amino acid sequence according to SEQ ID NOS.: 1-104; and
- (b) allowing the first polynucleotide to contact the second polynucleotide.

76. A method of treating a disease, disorder, syndrome or condition comprising administering a modulator to a subject, wherein the modulator binds to a cell surface molecule that is over-expressed in the disease, disorder, or condition, and is linked to the antibody of claim 35.

77. The method of claim 76, wherein the antibody is capable of initiating ADCC.

78. The method of claim 76, wherein the disease, disorder, syndrome or condition is cancer and the cell surface molecule is over-expressed in a cancer cell.

## SEQUENCE LISTING

&lt;110&gt; FIVEPRIME THERAPEUTICS, INC.

&lt;120&gt; NOVEL MOUSE POLYPEPTIDES ENCODED BY POLYNUCLEOTIDES AND METHODS OF THEIR USE

&lt;130&gt; 08940.0012-00304

&lt;140&gt;

&lt;141&gt;

&lt;150&gt; 60/485,217

&lt;151&gt; 2003-07-08

&lt;150&gt; 60/485,539

&lt;151&gt; 2003-07-08

&lt;150&gt; 60/476,621

&lt;151&gt; 2003-06-09

&lt;150&gt; 60/476,632

&lt;151&gt; 2003-06-09

&lt;160&gt; 104

&lt;170&gt; PatentIn version 3.2

&lt;210&gt; 1

&lt;211&gt; 2145

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 1

```

aaacagggtga cacaggagta gatgttgtct tagtcagggt ttctattcct gcacaaacat      60
catgaccaag aagcagttgg ggcggtaagg gtttattcag cttacatttc cacattttctg    120
tttatcacca aagggaagtca ggactggaac tcaagcatgt caggaagcag gagctgatgc    180
agaggccatg gagggatggt ccttactggc ttgcctcccc tggcttgctc agcctgctct    240
cttatagaac ccaagactac cagcccagag atggtoaac ccacaagggg cctttccccc    300
ttgatcacta attgagaaaa tacctcacag ctggatctcg tggaggcatt tccacaactg    360
aagctccttt ctctatggtg actccagctt gtgtcaagtt gacacaaaac tagtcagtae    420
agatgtcttc atggagaaga gagggtgagg attgtaacta tctggggaga gaagccgggt    480
gggtgggata agatgtgcga tgatcttttg tgtaacattc tcacatactc ctcaatgact    540
tatacatgtg attccaagcc cagtcacagc aatggactaa gtcatttcct ttctcggggc    600

```

WO 2005/005597

PCT/US2003/027106

```

agggttctga cagtgtatgg agagtagagt agatttaaga ttgcccatct tccctggttc 660
tctgtggta cgtctgtctg ggactcagtg cacatgcctg tcttggggagg tgcgttagct 720
cttccctgat gccatttctc aagctgtaga gtttccctc gtcccttga acagagccact 780
gtcgtctggg taaggggact cccctgcctg cagcaaggca ggactattgt gttccctcct 840
tagttctgtc ttccatctgt taacagtggt gctgctgct ctttatgttc atagtctgac 900
gagggaggct aatgacccac agtggggctc cagggcctaa ctgcctatgt ccttctcttg 960
cgttgacca tgagacttgg gctcatggcc tctctctgct tccctgggtc agtgtgggta 1020
ggcagaggga aaggctctgg tgaggacaag gctttgctga ccattctgct gcttctcttg 1080
gtctctctgc ctgtctgct ttctcctcct tcttctgttt cccctgtttc ctctcctct 1140
ggtaccttct tcccccaacc tggagagtgt gctggggttt acagcgtgca tccctgcctc 1200
tcaactcagga acaggtgtgt ggcctctcgg ggaactttga tggcatccag aacaatgact 1260
tcaccactag cagctctcag gtggagggaag accccgtcaa ctttgggaac tctgtgaaag 1320
tgagctcaca gtgtgctgac acgagaaaag tgtcaactaga tgtttccctt gccacttgcc 1380
acaacaacat catgaacag acgatgggtg actcagcctg cagaatcctt accagtgcg 1440
tcttcacagg ctgcaacagg ctggtgagac tttgtgggta gagaggaggc aaaatgatcc 1500
aaaggcttgt gctgccttg agtgtcagtg tccgatgtga gcaccaacta ggctggagtc 1560
ctgcaagggg tcaccacaat agctctttct tggcttctag atgagaagag catgcatagt 1620
ctttgaggga agcaatggct ggccaagcgc ttctcttgta cgcaagaagt ctctgtctct 1680
gaagtctct ctgcattgcc tccaatcaga gccagggaat tctttcctt gttactgttc 1740
tacgggtcca gacccagcca gaacctttcc aatcatcaac cacaagcaaa tcagcaaaact 1800
gcctctttag tgcacagtc ccttctcatt caaactcgtt ttctggcatt aagtccagtg 1860
attttgagtg ctgctttttt tttttttctg gcttcttttc attctctctg ctccacacatt 1920
tcatagcata taacatcaaa caatagtgat gaattctcca cagttaagtg gacttctttg 1980
ggcatttgca tgcacgtcgg cacaagcatg tatgattgtg tctctacaca aatgcttate 2040
cattgtgcac ctgtgtggt tcccttaaac atgattgatg gggtgagtc atgtatctca 2100
ttttttttt agctctccag agacttccag ccagaaaaca gtctct 2145

```

**PCT/US2003/027106**

Page 235 of 449

WO 2005/005597

PCT/US2003/027106

```

atatttttag aactactagc tttccacag ataagcaaat ggggattcct gagggagctg 1500
ctccaccgtg ctattaagac tctggcagga tggtaggatg tagatcccta tattaataag 1560
tcctgtaaat acagtgctct agggctttgt atagctgtcc tagactacag aagtgctctc 1620
tgattaaatc caaagtctgc cattgttaac tccatagtgc tgtagcgaca cgttttatca 1680
tggcgcctct tctatgtttt gctttgcttt tctctagagt gttcatctct cctctgatga 1740
gataggaaag ctatggaagc aattagggtt cccaatgac tatgtgacca agtgtggac 1800
agccctatta aagtggtaaa taacttcttt ctttaaccac tcgtcctctt tgtctgccat 1860
ttagttttat agactctctt ttaactaaac cgagagatca cgagactacg gaggtctatta 1920
tttccaacaa taatatTTTT gaaacttaga aactcattaa tatgattgta gtaaaatato 1980
caattacaat ttctgggatt ccatgtgggt cactctgata atatatatgg ggctcacaca 2040
cacacacaca cacacacaca cacacacaca ccaatgagag gtaaaaaaca acaaaaaact 2100
aaaatcatt atccctgtct ttttcgagtt actgagctga gaggtaagag gtaaacacct 2160
acttaaggtc tagttttcct ggggaaaatt ttaatgggat ttacactcc gatgtcatct 2220
cacaactgca gggttttttt tttcttccca aattattctc tgtcatctgt gtttttagag 2280
cctcttagta aatcacagca ctgtagtccc taagtctgta ctttttagga tcaaaactca 2340
agtaaaactc aagattacct cttattatac ccagaaagcc tgaagttaa ttgaatgtgt 2400
gaagttctaa cc 2412

```

&lt;210&gt; 3

&lt;211&gt; 2627

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 3

```

gctttttttt tttttttttt gcttgtattc tggacttaaa gtcacagccc tgccctgaac 60
ttcactagtg ccagcatctc gtccaaatc tgcctcccca ccccttctc accttctctc 120
attcctgccc ccaacggggc attctgcttt cactcatcac tgccaccttt ttgtttctct 180
tccccgattt agattttcgt gccagacgtg cagagcagcc atctcatttg gtaaacacta 240
gatgaacact tcttaaatag aagcaacatc ctttccagct agctttgtta aaggggcaga 300
gaccgttcag cccatcaaac tgatggatta aaaaaaaaag taacatgtaa gttagaaaaa 360
tacttcagga aagatgtgcc atcattatca gttcctcaag ataactcaatt agaaggaaac 420

```

WO 2005/005597

PCT/US2003/027106

tcattgacca ctaagtgtgg aactcttccg aaagcagcag gtgaagggga agcaactcct	480
ggagcccacc tgccatcaag cctgttccca atgctgaacc tacacaagag gcaatagaac	540
cctatttgag ggtcctgact tttctgttca gtatctgcca tagatgggct acatcaaagg	600
aaagattggc tagcaaacca gtccaaatct atgacccttc ttttaaatg gatcatgagg	660
gccttaaac atgggtcaac tgcaaatgtg cataataact ttgcttccca agttcttcta	720
tgaatttgcc tggaagtggc acaccttga agaactgtg tgtgtgtgtg tgtgtgtgtg	780
tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tatttatgtg tttgttttct ctgtggaatc	840
ttgaacatct accccttttc taccttagtt tatttaocta tcaaatgagg ttgaatatat	900
gaaaacaatt attaaattgt ggaaattcat gtgaaattta ctaagaaatg acaacaacgc	960
tgtgtataca gcaaacactc aataaatttt aataattatt tcagtataac cacaattact	1020
gtataaggat tgaagacat tacagacaat atcatgctg cccctgagaa agattcgcaa	1080
taagcactgt actaaacgca tacatttttt tataatcact tgatagcaaa ggtagtttcc	1140
actggaaaa tgcaattaa agctcctaaa acaagcaaa actgtgtgtg gtgtatgtgt	1200
tcatacagtt tctaaagaca gaaaattcta aaactgactc cccataggct gctactccaa	1260
gaagctgtag aactgccatt aggtctaagt ctgtcttca gaaaaatcca tggaaagtgt	1320
tagcagagaa caatccaggg gaagtactg tagcattcag aaacctggcc aggtggcttt	1380
caaggtctga gaatgtgagg gaggaggtat ccaaaagtag tctctaaaag agccacaggt	1440
catgggcagc tccaccaggt tgatccccct atctttgctg gctcagctac ttgtccttgg	1500
cagatattcc ggcaatgcac tctgttgaac aagagtgaat gggagaactt taacacgggc	1560
aaaaagaaa cttagcaacg ggggaaaaag tgagtatttt ctaacaaaag tcaatgcctc	1620
taactagatt ttatagtttg ggttaaaaaa tttaaatctc tcttaagctt taggtgggtg	1680
ttctctctct ctctctctct ctctctctct ctctctctct ctctctctct ctctctctct	1740
ctctctctag ttaatatatt atttacttag caaatgttg ttgaccattt atcctgccac	1800
atgtcaggat ctgctatagg aaagaagata acaattccaa ccttgatgta ctgtgtgaaa	1860
gagaacatga gtttgtatat agaacatgct tgatacaatc attagtagcc ataccattgg	1920
ctacaatcat tgagacaatc attaatacca tcggctagtt aatgattatt atacttttagc	1980
ctgcagtact ctcacatag agcttaacaa ttatggattt ttctctggagt aacaccata	2040



WO 2005/005597

PCT/US2003/027106

```

gatactccag ttctgaaggt ataaaagaaa gtgacatagg aatgtgcatt tttaatggct 2100
gtaataactg actgtgtggc ccatgaaatg gaacttcaag agaagtgga cttttcttca 2160
tgtttctccc aatttccaaa tgaagattca aagcctggat tcaaaggctc cttgactcta 2220
ccggcctctc aatgctacat tcaatgtctt gattgataag aacaatgtgc atatgaccag 2280
gaatgatagt aaggtaaaaa tgtgtttgta ttgcccatt cccaagtta cttatgatac 2340
ctaaaggagg ccatgattga cagatcatca ttatcccttg aataaatgtt ctatcataga 2400
gtacattgca tgtggcttta agatttgctt agacaaaagc agataccata catctataat 2460
cctgtgtctt gttttattct aataaatgtc tccaagtgtc tctcaattca actcacctat 2520
gttactcttc cctgattgac agtgttctgc atggctgtta tctttccga tttagtcact 2580
tctcttaaat agacactaag agtatctttc agaagctcct gagagac 2627

```

```

<210> 4
<211> 3153
<212> DNA
<213> Mus musculus

<220>
<221> modified_base
<222> (1410)..(1410)
<223> a, c, t, g, unknown or other

```

```

<400> 4
ccccatcct tgctaaact ctatgatagg tctctacatg ttctatctcc cctttgttgg 60
gtatttcagc ctatctcacc cccctttggc cctgggagcc tcttgcttcc ctggcatctg 120
ggaattgctg gtggctatat ctatgtccca atccccatt gctactaaat accactgttc 180
aatttctcgg cactctgtat atccccctg cctctccca tacctgatcc catcccaat 240
tctcccttcc ctctctcttt tctctcgaag tctctccca ctaacttccac aagagtattt 300
tgttccccct tctacacatt tcagtggtcg ttctcttga cctacatatg gtctatgaat 360
tgttaatttg gtattccaag cttttgaaca aatatcaacc tatcaatcag tgcataccat 420
gtgtgtctgt ttgagactgg gtcacttcc tcaggatatt ttctagtccc atccatttgc 480
ctaagaattt tatgaagtca ttattttaat tagctgagaa gtattacatt ttggaagggt 540
actacatttt ctatattcat tctctgttgg aaggacacct ggggtctttc cagcatctgg 600
atattataaa taaggctgct atgaacatag tagaacattt gttcttgta tatgtctttt 660

```

WO 2005/005597

PCT/US2003/027106

gggtatatgc cctgtagtag tatagttgta tcttcaggtc caattttctg aattcaatta	720
tctgagtaac tgcagactg atttccagag tgggtgtact aggttgcaat cctaccaaca	780
gtagaggaag gttcttctct ctcacatcc tcaccagcat cttctatgtc cagaattttc	840
gatcttagcc attatgacta ttgtaaggta gaatctcagg gttgttttga tttgcatttt	900
cccaatgatt aaggatgatg aacatttctt taggtgcttc tcagccactt gagactctc	960
atttgagatt tttgtttgtt tgttttagtt ctgtaactca ttataatat gggtattttg	1020
ttctttggaa tctaattggt tgagttggtt ggatattagc ctgctattgg atatagggtt	1080
ggtaagatc ttttaccaat ctgtaggttg ccattttatc ctgttgaccg tgttctttgc	1140
ctaaataaaa taaaataaat aaataaaaa aaacttttca attttatgag atcccatgtg	1200
tctatagttg aacttacagc ctgagccatg ggtgtactat tcaggaaatt ttcacatgtg	1260
ccattgtggt caaggctctt tcccacttcc ttttctattt gattcagtggt gctcgtgttt	1320
atatggagggt ccttgatoca ctgggactag aggttagtca atgagatagg aattgatcag	1380
tttgcatatg tctacatggc atgaccatan ggtgtgtggg ttttaattccg ggttttcaat	1440
ttcattccat tcatctacct gtatgtcttt gaaccaatat catgagggtt ttttgttttt	1500
tgtttttttg tttttatcac catcacactg tagtgcagtt tgtggtcaag agtggtttatt	1560
ctcccaggag tctcttattt ggtgggaata agaatagttt tcatatcctg cgtttctgct	1620
atacagataa tttagaatgc tcttctatat ctgtgagaat gagttgcatt tgatggggat	1680
tgattgatct ggtattgctt ttggtagatg ccattgtttt atgtaatgct gcaatcatga	1740
gaatggagat ctttctgtct tctgagagct ttttcaattt ctttcttttag agacttgaac	1800
ttctttactt acagatcttt cacttgcttg gtttagtgca taccagataa tttcatatta	1860
tttgtgacta ttttgaagga ttctatttcc gtaatttctt cctcagacta tttatccttc	1920
gagtagagga aggctactga ttgaaaaatt ttatatccag ccactttgct gaagtgtgtt	1980
atctgctata ggaattctct gatgcaattt ttggagtcaac ttaagtacaa tatcatataa	2040
cctgcacaga attatatcat gacttcttcc tttctgatat gtgtcatttt gaactcattt	2100
ggtggctaatt tgccttgggt agaacttcca gtacaatact gcatgtgtag ggagagagta	2160
ggcagccttg tttaatccta gattttagtg tcattgcttc aagtttcact ccattttggt	2220
tgatgctggc tattggtttg ttgtgtatgg taagtatggt taggtatggg cctttaatta	2280

WO 2005/005597

PCT/US2003/027106

ctgatatttc caagactttt tacatgaagg gttgttgat ttgtcaaat gatttttcag	2340
catctaaaga ttgaccatg tgggtttttt tctttgagtt cctttatata gtgattata	2400
ttgatacatt tccatatatt gaatcatccc tacatccctg agataaagtc tacttgatca	2460
tgggtgaatga tctgtttgat gtgttcttgg atttggtttg tgagaatttt attgaggttt	2520
ttattgcatg aatattcata agcaaaattg gtctggaagt ttcttgcttt gttcagttgt	2580
tgtgtgtttt tgggtatcagc ataactgtac cttcataaaa cgaatggggt ggtgtccctt	2640
ctgtttctat ttgtgaaat aatttgaata gtattggtat taggtcttct ttgaaggtct	2700
gatagaatto taaactaaaa taactctgctc ggatttttgt tgttgttttg agatgtttaa	2760
tgactgcttc tatttcttta gggtttatga gactatttag atgatttate ttactctgat	2820
ttcaatttgg tagctggcat ctgtatagaa attgtccatt ttatccatat ttcaagttt	2880
tcttgagtat agtcttttgt agtaggatct catgattttt taaattttct ctgtgcctta	2940
tagttagttt gactaaaggt ttactatatt tgttcatttt ctcaaaaaca acaacaaca	3000
caacaacaaa aaacagctcc tagttgtgtt aattctttat ataattctct gttaggttat	3060
tgattgtgtt ctgctccttg gggagaagc atacatgagt tgaccatgct taaaaagat	3120
tgtctctggc tgggtgtggg aaatgcctta agg	3153

<210> 5

<211> 2900

<212> DNA

<213> Mus musculus

<400> 5

gagtatcaaa ggcataaacc accatacact gcctccaaac ctgcttgaac atgaagcctc	60
agtcctgctg ccaagaagtg atttcgcata cacaacaaac acgtcaacgc cccacctca	120
gcacacagag gaaaatgcc aacaggttac ttacgaggag tcttctgttg ccttcgaaag	180
accccaacag gtcggcact gacttcttgg gacttgagc gagatgtttt gcggtgggct	240
tctgattgtc atcctgctct gtcttaccg cctttttctt ctattcttg tctttctct	300
gttttgtctt ttctcagct ttcttgcct tgcttttctc tcttgagtaa cttgtcttgt	360
tttgactctc tccctttttt cttcttctcc ttctcagggt tctcagactt ttcaagcttt	420
ttcgactcct tggcattctg ctaggggaag ctatccacct gccctcctc ctcacactga	480

WO 2005/005597

PCT/US2003/027106

gaggagggtgg gctggctgag gtcatacttg tcttcatatt cgttgctgag aattctgtcc	540
ttcttttttgg gcagcttccc ctttactggc ttgtgaggac ctggcacccg atttgggtcc	600
tgatggccat gttcccgctt gtctgtccgg ttgtcccgga aacggcttgt gccacaaact	660
cttcgcgctga cctcccagag ggtgggaggt ggggtggctg tgaagcttcc atagttggtg	720
gctttgtctgg gcctcctggt ggccttggtc ttctctctct gttgtcctt ccgaggtaga	780
gggtatagct gctctgagac ggagggggccc ctggcagtggt tcacctctgc tgttgacagg	840
ggcctgtggg agactgagaa gggatgcaac cgggatgtcc agggcctctg ggtagctgga	900
taggcagtggt tggttgtagg tcttgcggct attgtcacta cccgggatgt ggcgcagtg	960
gctgtcgtga ctggagcagg aggaagggtg gtggcccttg gagtgggggg aggctgagga	1020
gtggctgcct tgctggtggc ctgctttctc ggagcctctc tggtggggtg gacttgtgtt	1080
ctccttgggt cctctttctc cttatcaccc cccaggcctg tacctctgc tctctccacg	1140
ccctcgtttc cttcctggac tacatggccc tctatgcccg aggccttaca cttttggaca	1200
aaacctctct gctgatttt ctcgatcctg cggatgggac cttgatcaat gacctatac	1260
atggcttcca gctgacccg gtaagggtag cgtctctcca cctgcagagt cttttttaac	1320
agcaccatgc taaacttgcc cttctccagt ttcaagaagc tcatcagctt tgggatgaga	1380
ttgggggtcca gaggtgctc caggatctgc ccttcattgg tgatcctccg taccttgccc	1440
ccttcctcgc ctgcctgggt gaagagcaca atctgttgga tgtgccttcc tgccagctca	1500
caatacacgt cgtccttcag gaggtcctc atgaggcggt agtagccctc tgaggcgtga	1560
ggggctgaga tgaccatac cctgttcttt cctgcaaagc tggccaggat attgggagag	1620
ctagatccag aggggaatcg caacattctt gtccgagcag aagaccctc atctcggacc	1680
atctcacgcg ccgagctcct agctatgggt ctacactcag gtctgactgg aactccattg	1740
atacctgagg ggggtgggtc catggtcggg tgagctaata tcaacactgg tacactcttc	1800
ctcctttgga aaggctgagg atttgggtct tcctgggtgg atttctcaac tccaccagac	1860
ctcccgtgtg gcctcagata ccgagctgac ctactgtgta ttggagaaac caaaggtaact	1920
ttccgtccag tgtggctgtc gctatccaag gcaggagaat gagatgctga tccacacacc	1980
agccacatgg ccaagacgct ggtgaagtgg gggtccattt tccacatcat tgtattatcc	2040
acttggggac gcagaggggg tataatacaa aatgaaaat aacataaaat gagaagggag	2100

WO 2005/005597

PCT/US2003/027106

```

aaaaagaaaa gaaaaaaagt cattaattgc aagcagagct gggcatgac tctttctcta 2160
acttgcccaa aaagaagggy caggagatag ttaaagaaga aaaaggaggy caagcagaggy 2220
agggcaacaa gagagagggc ttctcttaaa ctgctgcgat tgtcagtgct tagcagagtc 2280
agtccttaag caggaatatc agctttgatt tacaggcgcc aggcagtagg cagcgctgct 2340
ctgcctcagc tgtgccaga tgcaccagag actgtgtaaa ctgagcatgc taattatgaa 2400
ttctaactgt gaatgtgcat tcacacttca tgtcttcaaa caagcaacaa ggaacaaaac 2460
accagagagc aaggttggca cacttacaca gtggttcacg gagatgctt cagaggcttt 2520
ccagagaaac gtgaaggttg gtccccagga cagtttctca ggtgagatcg gttccttctc 2580
gtctctctgc tccttgtctg tctgcaaagc agccccaggy agcccagcct gggccgatcc 2640
cttttgctgg ctgtgtcttt tacctctgg tccagtggga ggaggtgaac gctgctgtcc 2700
ttgggaccgt ttgtatctcc atttgtctgc agtttctcct gggctctgtg gtgcgggtcc 2760
ttggttgcca cagggatctt cctgaaagtg aagtcctagt gattttctga tctcgtcttt 2820
cccttctgtg gagttttccc agaactctt atcacccttc cctcctgca gtcctggcca 2880
gtccctttgt ttcogagcgt 2900

```

&lt;210&gt; 6

&lt;211&gt; 1852

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 6

```

atctctcttg atttctttct taagagaact gaagttctta tcatacaaat ctttcacttc 60
cttagttaga gtcacaccaa ggtattttat attatttatg acctttttta ttttttggtt 120
tttcgtgaca gggtttctct gtatagctct ggctgtctcg gaactcactt tttagaccag 180
gctggcctca cactcagaaa tcgcctcctc ctgcctctcg agtgcagaga ttaaagggtg 240
gcgctatcac acccgctctc ctttatgact attttgaaga gtgttgtttc cctaattttt 300
ttctcagcct gtttatcctt tgtgtagaga aaggccactg abttgtttga gtttaatttta 360
tatccaacta cttcaactga gttgtttagg agttctctga tagaattttg ggtgacttta 420
aatatactat catatcatct gcaaatagtg atattttgac ttcttccttt ccgatttgta 480
ttcctttgat ctccttttgt tgtctaattg ctctagctag gaactcaagt actatattga 540
ataggtaggy aaagagtggg cagccttggt tagtccctga ttttagaggy gttgcttcaa 600

```

WO 2005/005597

PCT/US2003/027106

gtttctctcc atttagctcg atgttgcta ctggtttgct gtatatggct tttattatga	660
ttaggtatgg gccttgaatt cctgatcttt cccagacttt tatcatcaac ggaggttggga	720
atttgcaaaa ttctttctca gcgtcccaag agatgatcat gtggtttttg tctttgagtt	780
tgtttatcta ggtggattat gttgatagat ttctgtaaa tgaaccatcc ccgcacccct	840
gggatgaaac ccacttgatc atgatagatg atogttttga cgtgtttcttg gatttggttt	900
tcgagaattt tattgagtat ttttgtattg atattcataa gggaaatttg tctgaagttc	960
tctttctttg ttgggtgtgg tttagatata agagtagttg tgacttcata gaacaaactg	1020
ggtagagtac cttctgtttc tattttatgg tatagtttga ggagtattag aattaggtcc	1080
tttttgaaag tctgatagag ctctgcacta aacccatcag gttctgggct ttttttgggt	1140
tgggagacta ttaatgactg tttctatttc tttaggggat atgggactgt ttagatcatt	1200
aatctgatcc tgattttact ttggcacctg gtatctgtct agaaaactgt ccatttcctc	1260
caaggttttc agttttgttg agtataggct ttctgtagtag gatctgatga ttttttggat	1320
ttctcagat tctgttgtaa tgtctccttt ttcatctctg attttgttaa ttagtatact	1380
gtccctgtgc cctctagtta gtctggctaa gggtttatct atcttgttga tttttctcaa	1440
agaatcagct tctggtatgg ttgattcttt gaatagttct ttttgtttct atttggttga	1500
tttcagccct gagtttgatt atttggtgcc ttctactcct cttgggtgag ttgtcttct	1560
tttgctctag agcttttagg ttgtctgtca agctcctcgt gtatgctctc tccagattct	1620
ttttgaaggc actcagagct atgattctaa cttttaggga ctgcttcatt gtgttcata	1680
agtttgata tgttgtggcc cctctcatt aaactctaaa aagtctttaa cttctctctt	1740
tataaccagt ctcccaaca aaggaaagat aaggaaatc tgactgtgct cttctttcca	1800
ggggggcatt cacactaata ttaggctta agtgatttgc ttcttttaaa gg	1852

<210> 7  
 <211> 2417  
 <212> DNA  
 <213> Mus musculus

<400> 7	
ggtgaagggt gccctaggat gtctaagaac atggctaaac aagccatggg gaggaagcca	60
ctgagcaacg gtccttcaga gccattgtct tgttctctgcc tccaggttcc tgctctggct	120

WO 2005/005597

PCT/US2003/027106

tcttccttca gtgatgcccc gtgaactgta agatgaaaac aaccctttcc ttccctgatt	180
gcggttgatc atcgtgttct ttgcagcaac agaaggcaaa tgaggacacg gaccattagg	240
tctaactagc cctctctacg tgtatttggg ggcgcgacc ctagacaatt acagtaccca	300
tcacattggt gacactggcc accatggcta ggcatgacag ggaagcttca ggcactccct	360
ttgccagggg gttctgagtc tggaacaagc ttctccttaa ctcaagggga gttcacgctg	420
ctgagttagc ctggagacat ttggggctcg tggacagtga agatggatgg tgtctacagg	480
atggtgtggt tgggtgtgac agcaactgac atgagctggg tgtgggactc aggcattact	540
tggatcagct cattcagatc accacagctc tagcaagaca gtggcaacat tgccctcttc	600
tttagatggg agactgtgtt gctaaaactc tcatcagact gttgatggta gcatcgggt	660
ttgctcacct ctgcaagtga ccatgaccag gggatgagat ctctctactg acaagcaagc	720
aagtcacggg cacttgtggc atacaatatg gcccctgttc ttctgttact cttcttatta	780
gataaaaagt gtgaatgttt gtgtgtacat gttcatatgc atgtgtgtga gcatgtatgt	840
atgtgtgagc atgtatgtgt gtgtgagcat gcatgtatgt gtgagcatgt atgtgtgtgt	900
gagtgtgtgt tactcttctt attaaaaataa gaatgtaaat aaaatgtgtg tacatgttca	960
tatgtatgtg ttgtgagcat gagcatgtgt gtgtgtgtgt gtgtgtgtgt gtgagagaga	1020
gagagagaga gagagagaga gagagagaga gagagcattt gtacagtgta aatgtcaagt	1080
gtcttccttg atctcctccc atcttgtttt ttgagatgaa atctctcact gacctggagc	1140
tcctagactg tgtagactga caaaccacg atgctcagc cattgcctcc tttagcaggga	1200
atcatggatg tgcaagacca cacatgtcct ttttcatgga ttctggggac tcagtcaccag	1260
gttctatatt tgtgcagcaa acatttttatc agctatgcca tctccccgga ctctgtgttc	1320
atttattgta atgagtgtat tgagctaatt gtgtgccctg attcagatct cccgggttaa	1380
cgtgtaactg ggaccactgt tcaaggcata tggggcagaa gttctgatcc atttttaggtt	1440
ttccagagtg gcaggagagt taggtaaaaa ggtcagcaat gacaaatgta gagtgcacaag	1500
tgcttcacat acatgcagac aaagatatct gttcccccaa gacacctggg ttgtcactga	1560
gaaaatatcc acaaggcaaa acaatgccac gtgggcaaac ttacctacct tcagccttgc	1620
tattggagcc attcactggc tgcctaccag aaacacagga acggagtgtct taccctgtgg	1680
ggtactggga ccagggtata gattcctttt atttgtctgg acatgaattt aagctacaga	1740

WU 2005/005597

PCT/US2003/027106

```

acctcacaac ccattacaca ttgaagaact cactatatcc agccaccagc catctatcag 1800
gtgaccactg agaggttcca ggacccaaga aaaccaogag tgtgtgagcc tctctcctcc 1860
acagtgtcgg agcctccccc tatgtcctat gctcccgctg gatcacatcag cacatgcccc 1920
acctctggggc ctggcccacc ctttggccac cgtgagggca caaatgagac ttggagtcac 1980
tccagcacct ctgctctgga cgggcccgtg aaggaggagg ttgtgtgttg atgaatcaat 2040
agtagtgagt gactctcatt ccacggcagg aattccaggg atacaaacac acatctcaga 2100
ttaagaaca tgtgctagag catgaagtag cttatcaca ccattaccg totccagcgc 2160
agacagaatg acaggagaga ctaggcagag gtcacagggg gtacatttgg ccatcaaaag 2220
ccgtatcgac tggagtccat tatgacaacc tccagtgaa aagggtggaca ggctccggag 2280
cattagttag ctcccaaat acaagaaat tgatccgtga ccaattaac ctggcagctt 2340
tcattttcga tttcctttct gattatacgg aaccattaaa atgaacccaa atagaaagga 2400
atgagatggg acatcgg 2417

```

&lt;210&gt; 8

&lt;211&gt; 1298

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 6

```

gactgtggcc aggtgcagcc aagccactct tgcggcgct cgtatcctta gttaggtggc 60
gaaatgctga tgggtctctc tattcggggg aatgcggtag tgatgtataa ggtatgaaag 120
atgtggcctg cagagagcgg gcaactatct tactgctgct gctgctgcca ccgctgcctt 180
tgctgccgc actactgcgg ccactagagc tgcggggagt gagcctccct tcttccagat 240
accagctcc gttgcactc ccgctccctg gcccgcacg gaactcccg cccaggga 300
caaaagcaga gtcgggtgct cccctgttct gcagccagag gatgatgtgt cgaggggct 360
gagcagagtg tggctcttcag cggctggaag ctgctccctg cctttctctc atgagtcctg 420
actcgtggcc ctggcaatct cagaagagct tcaactgaatt ccttccgac cagaacctgg 480
gaactcactc ccccgagcat caccctgtg cagcctggac acaactgact aaccaacttt 540
taggacattt cattcagtaa gacatggtgg tgaaccaagg ctctaaatct tcatgattga 600
aggactctta cacaaggcaa agatcaagat gctctttcac tcagtggttg atctccactg 660
tttctgcaca tctcatctga catcatctca cctcttagaa tgagatggca tttgctccct 720

```



WO 2005/005597

PCT/US2003/027106

aaagagtttg atggctcaag catggtggat taggcctttt ctgctgggat gctatgactc	780
catttacatg tatgtgtctc tctactatc catggcctc tgaatgggg aaatcacatc	840
tttctattgt tttcctgatt gtaacacag taccacaac atagtgaagt gttaggatc	900
tgataaacaa atctatcaat agatttgga aacggggtag ccctgtaata ttctatggaa	960
agagtaaaat atatgcaaat gtggacagat ggtgtctcct ctctcaattt aaaaacacaa	1020
agtgtattat tagtaagca caaagaggaa aaagactgta cgtgggagtg ctgtaagaa	1080
actggctggt gaagagatgc aaagacttca atagatttat tcatgcgctt acagataggc	1140
agcttttttag tccatggaca ttctcatcct ctgtacaatt gctattgaca tgccaatgag	1200
ttccacattt ttctgtccat ccttactgaa ctacgggctc ctcttgcatc ctcaaacatc	1260
ttctggatat attctggcag attaagtttc aaaaatcc	1298

&lt;210&gt; 9

&lt;211&gt; 4319

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 9

acacagtttc gaagaagcgc ggggtgccgc caaaggctgg agtagcgaga acgactccca	60
gtctagcggc tgcgcgctcc tcaacctgca gaccgaaagc tcgggaggac ccggcctagc	120
ccgcgagaac tgggtgggtgc tggaccagag catctagggt ctctaagcgc gagactccag	180
cttagccaga gccctgtctc tctcggggcg caacaacttt gaagatctat cgcggacaga	240
gtctcaaaac agacaacacc taagctggcc actccctoga agagcccgat ttggagagtc	300
tagatgccaa gctcagaagc agcaggagcc tcaggccaga aagtgaacc cgggccactg	360
ctgtgaagca gcttctctt agccaatcca ggggtctggt ctctctccat tctgaacaac	420
cgccatatgt ttcctcagac ggaacaagtc tgagaccagc agatgaacag gcagaggcct	480
gaagacccca ggaacagctc tgccttctct gttccttgat cctctctgt caatcatcat	540
atctactagt gacatccgc cccacgaaa gctgcctgga gacaagacgc atggagaggc	600
ccaccagcaa ctggagcgca ggcagctggg tgcttgcaact gtgcctcgcc tggctgtgga	660
cgtgtccgac ctctgtctcc ttgcagcctc caacatccgc agtcctagtg aagcagggca	720
cctgcagagt gattgtgcga catcgtcgtc gcaacgggaa cgcattgag gagcgtccc	780

WO 2005/005597

PCT/US2003/027106

```

agacggtcaa atgctcctgc ctgtccggcc aggtggttgg caccaccaga gcaaaagccct      840
cctgcgttga cgcctccatc gtccctcaga agtggttggg tcagatggag cctgtcctgc      900
tgggagagga gtgaaggtg ctccccgacc tgtcaggggt gagctgcagc agtggacaca      960
aggtcaaaac caccaaggtc acacggtaac tctcggaggt catggcttag gttagacagc     1020
cttgacttag ctctgggactg aagaagggcc tggtcaccag acagcagata agaggactta     1080
cctggacatg tgcctcatgc aagtgttaac tagaccggcc agggccccctg ggcagcactc     1140
tgttcagcta aaatgcttgg atctttggcc acacacttga gagacctgtg ctctcctatg     1200
aacaaaagtca acacacaaac ctatccttaa ggaatatctt gtcaagttaa ggagtggatg     1260
acaggcaatt tcaacagttt aaagtgtttg gtaccgtggc ttctgagcga cctgcagtgg     1320
gtgtggttgg gtggggcgga tggaatttac acagatcttc agccaccoga tcccaggaca     1380
caaaagtatg agggccacac cagtatcttc ccatcttggc ctcccatca aactgcctc     1440
cccagcaaga tgctaagatg tgagaggaag aactgcccc ctgggtgcca gccagtggga     1500
tctcttttgg acagcactgg aaagtagaga tgaaggggtt ctccgcaca cctctgcaga     1560
ggcagggggc gggcgccatc cccatgctgt ccatggatgg acaggacctc agtcagaatc     1620
acccctccac cttgaacttc ggggtgtttg ttgctgtttt aaaggacgag gaaaccgagt     1680
cacagaggat gagatggatt tgcccaggat ctcacagctt ggccttccaa aaacacggat     1740
gttaggactc cagcctaggc cttccgtggc agttttatct agacagttag accccgcaaa     1800
cactgtcttg atagaccaa catgattctt gggagatggg actttgacca ctggaatttt     1860
ggttagggcc actgatcttc catcaacaa acaaacaaac aaaccctaga atatacacac     1920
acacacacac acacagcaga gtggagctcc ttctcagtc cccaaggcca aacaggcccc     1980
gtgacagccc agaggtoctg cagcccagcg gcagcagaag cagtgtgagc agttaggtat     2040
cccatoaccc actctgcttc tctatcagga gcttcagcca gccccctaca taggtacctg     2100
ccaggaggca gaggggcagg ccagaggact tcataaccag gctggcctcc tagatggctt     2160
gggagtagca agctggctta cttttattac caaggcctta agtgttagag tgagtgttag     2220
agaccagcct ggatgatggt tccctgagaa ggtaaatacag ccatagttta cactggaatc     2280
ttggtgcctt tctccttgcc tgtgtcccaa tgcatttgac taagactctg gtatcacccc     2340
acctcagggc atgttttggg ttggcaaaa tgagatgaac agtaacgtta tctttcaaaag     2400

```

WO 2005/005597

PCT/US2003/027106

gcaggcctct gtcagtcctt gcttgtagca cggtagcagg ccagggtcac caagggtcaa 2460  
 tggcagtcac ggtctccttc agtactgagg agtggaggcc agagggtgtg ttaagtctcc 2520  
 gtgacatatt ctttgttttg ttgttttgc tctttttgtc tttaaaaaca ttatagactt 2580  
 gccaatgcc a tctttagctc tagggaggga aggaacacat tgttgcccat gtcagggtctg 2640  
 tgacccttec caggggagct cgaaggcctg ggtaggcttc ccagcctctt ggctcacctc 2700  
 ctgtaccatg gaaacotgag cggcagggtc ggggtctggg ttgttttctc cctgatgtct 2760  
 agagagagat gtgtgagtga attatttagg ttaocgtctc agcagagcca gacagtgaac 2820  
 gcctgcttcc ctggaggcaa aaggtagtct tctggggggg tgtggagcgc catagactct 2880  
 ctgctcactc tgtctggac actgtcacc aacggctcgg tcccctgctc tgccccacct 2940  
 gtgttgctca cagcaactgg gttagagtgg agagttcaga gatgacgcgt cacaagcctc 3000  
 cgagagcgcc cagtctcttc cagctccccc ccaccccccg ctgcctcggg gtctctgattc 3060  
 tgtacctctc ctgaccccca ctaagttgg ctaattcctt gtttaagtctc cctccctgcc 3120  
 tctgacctta gccatgcatt tagtgggtga actctgagct gagtgggtat ctgtagattt 3180  
 ccagggaagc cccacacaaa aagctctggc aaagaaaaa tccagacccc cactccaac 3240  
 tccacccccc cccaaaattt gtatccagct gaatccaaac ctgtgtagggt tttgtagcta 3300  
 tgcaaaagac agcttagaaa taaatggagg gttttttggt ttggttttgg gggggggtt 3360  
 agagcatagg ggttcctcca gtcatttgac ttctctgccc ctccttgacg agaacatctc 3420  
 atcatctgag gtttctgga accccatctc ttcagctatg cgggctctag gaaagccagc 3480  
 aactactaaa tcatgtgact gatttctgct aacctctggt cagtgttact gagtctgtga 3540  
 gtgacatctc gattaatgat cccagacagc tccacacat tgacttgac attgagacga 3600  
 cagctcccta aaccagaat tatagttgca agagggttta gaagccaact ctttgatttg 3660  
 ccagcctggg agagggtagc tcagaaaggt taagtaattt gcccgagtc acacagcaag 3720  
 ctggtggcat gtcctgtctc agtgactcag catagagttc ttccactat tgtacatccc 3780  
 attgtacccc agagcatgat agaacttggc aggagaacag ggttcttaac tgtgagagtc 3840  
 tcattctgga atcgcccaac actgtgagag caagggccag agggagaagc agcaggaaac 3900  
 acatagtgat cacatacaca tagggaagca agaaggggag ggggtgatgc ccagaatttc 3960  
 aaactacaga gtcaaaccca acaggacaaa tgccacacga aggagaactg gtgcctgtcc 4020

WO 2005/05597

PCT/US2003/027106

tttcctgagg aggcaacatg gagtgttgtc agtccttgcc aaactgggtg tgggggtgca	4080
tgccatatac ccaggtactc aggaagcaat aaggaggatg gcaagatgga ggccaggctg	4140
gacctaacag agaccctgtc aaaagaggaa caacaataac aacagaaaaa gaatggaaac	4200
ccttgacgaa ccttgatgtc gtcttgatca cccagggtc tttttgtcct atgcagagga	4260
ttgcaacta aagcacatag gttacttttt ttttaacaaa taaagtttta ttgaaacat	4319

<210> 10  
 <211> 3423  
 <212> DNA  
 <213> Mus musculus

<400> 10 ggctagactg aaacccccag aggctggccc ctaatggccc aagtctgccc tacttctcaa	60
aaataggcta catcccacag cctgtcaaaa tagtgccacc tactggggac cacatgttca	120
aacctaggcg cctgtgagga gtatttttgc ctttaatggg taacaattct caactgttc	180
ccacaccaca aacatagctt atgtgagatt tggtagcac ctgagcacag ttccagcctg	240
ctagtgtgac acttaaatgc agcagccaaa gtccaagagc acacactgtc tcttgaggcc	300
agaaccccg cctcttgagg catcaccccc cggtagccatg tttcttcccc ccacccccac	360
cccgaaatatt tcttcagcct ttaatgttct ctctgttctt cctcagctat taaatctctc	420
aggtagataa tattcatctc tacttatcag gactctgtaa gtctatctca tgaactacat	480
ttaaaaaaaa aagatttatt tattttagta tgtgagtaca ttgtacctgt cttcagacat	540
accagaagag ggtatcggtat ccattacag atggttggtga gccaccatgt ggttgctggg	600
aattgaactc aggacctctg gagagcagtc agtgctctta accactgagc catctctcca	660
gcccccttat gactacacct taactgagtc ttccattcac tcaactaaatc tcttttccct	720
tatggcccac acggttggtt ttccccagg tatctgtgta aattttactt aagtcttaga	780
cagctttggt gttttgcatg gtgtttataa ctggcatctt caacttagat ccagttgttt	840
gtactgaaca aatattttga ctttcaacac aatgtcttac gttgttgcta tgataaatgt	900
ttagtgttct gcataaatat cccaatagtg gagagatctg atgagagagg agagaagaaa	960
gaggctcatt tcaatgatct gctgttgatg ttttgaaatg tcttagcagg acttggtggt	1020
ctgtctctcg actgagggaa aagcagttgt tagcagtcac ctgtcattct cctggcacia	1080
atcttgagcc caagtaatga agcaattctt cacagggttg agggccacag gaggctgcac	1140

WO 2005/005597

PCT/US2003/027106

```

agtagtctca gcagacagcc agcttcattc aggaggcccc tgacatctgt gtctccctcg 1200
atgaccacct gtgcacactt tctcagagga agaagagaga tcatccctta aagccaaatg 1260
tgaaacgagt aaatgattaa gtccatgcag tccctaaggg cccattcact ccgagtcac 1320
attgaatgaa gcttcaagac agatatggaa atggcagtc cataaccttc tggctctaca 1380
aggcatcact cattgtagtg ggccagagca gcattgcccc atagcaagac acaggaggat 1440
attcccacgt gtctccatat tgtaaacaga gtaatgttat aattttttgt cagaataaaa 1500
gactgacttc ctttaggcag gtttgtctgt ctgctgogtg tagtgtgtgt gtgtgtatag 1560
acaaagatga aaagagggat tccaagtcct ctggagctgg agttacaggt gtacagagct 1620
gcctgaggtg ggtgggtgct gggacccaga ctctggtcct ttggcagatt aggaagctct 1680
ctaaacaaac atctgagtta tctctccatc ccataagca ggctttggaa agcagaacta 1740
taccaggcta catgtaattg ttttacataa tctgctgcta tactgcccta tgtaaatata 1800
actatttata gtgccccccc actctgggaa ttatcacttt ggcttacttt gctatggatg 1860
acagacgtgt aatagaatcg aactttttta cttgaatttt ttatatattc tgggtaggga 1920
gagttttgcc tgtgataact gatggtctaa cctgaattgc atgctttcat tgtgcttgga 1980
tgaattcttt atatatattg aaaatccagt ttctatagaa tcttattgct gcaagcttat 2040
aaaatgtcag atagggtgtt tagcattttt tgtgtgttat ctaatttaat tatcacagta 2100
tctctgtcac agggcattct gatatggtgt ttaagtattg aattgggtgg ttcttggttt 2160
aagttctgat accactgttt cctcttgtga ccattggtaa actttatata tcttgcaagt 2220
cttcctttgt gttatatatt tattttgtgt ctgctgtctt gtaccacctc actgtctata 2280
tgtgaatgta tgtatatata tatatatata tatatatata tatatacaca catatatgtg 2340
tgtgtgttat gtatgtatgt atgtgtacgc atatgtgtat gtacatatgt ttatgtgttc 2400
atctctctat gtctgtgtgt gtgtctgtgt gtatatattg gtatctgtgt ctgtatgtct 2460
ctctctctct ctctctctct ctctctctct ctctctctct ctctgtgagt gcatgtgtgt 2520
agaagtaaga ggaagatgca ggcacattc ctctctgggt tctagggttt gaactcaggt 2580
caccagggtt ggcaagcatc tttaacctcc gagccatctt gcctgccag ttctctctcc 2640
tatgtattgg aaataactgt ccctgtctta catgcttgta aggattgaga gagtgcatat 2700
gtgcaccatc atgtacacag cacacactca tttaatatcc attgagacag tgggtgtttt 2760

```

WO 2005/005597

PCT/US2003/027106

```

ctcttttttc cctgggttaa tttaggtga gaaccaccag tctagctggt ataaggaaa 2820
agacccatgg gctacttttg aagtaaagg ggatttattt aggcttagaa ttttggaagt 2880
aaacctaaag ctaggcagcc cattacttta gcccttgcc gccatggcag gagcacatgg 2940
gcaagtaagt gctcacttct ccagccagga agcagcgtga gagactgact cagggtccac 3000
agtctcatgg gcatagctca aggtctcagc ttogaagatc agcagcacct acctaccaga 3060
ctgcccacc tgggtatoga attctgacct ctgagggggc acccagctct aaagaaaacc 3120
atctagctga ctctatcaa gctgctgttt ttatagaagt tggtaaccaa ggcttaaaag 3180
tatttgaatt atttcagtt ctgtgcttgg tgctcaccaa aggttacagt gttgccaaac 3240
gtcaagcagc tctgtgtggt tgggtgccagg gacccatgca tggggtaggg ctcagaacct 3300
gcagtcccta tctgggtact cagccagcct ggagcagatg aagctgaggc atgtcaatca 3360
actaggagag aatttcagtt gggaaaatag ggaatgccag cttgtgctca ggctttgggt 3420
ttt 3423

```

&lt;210&gt; 11

&lt;211&gt; 3340

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 11

```

gctcttccgt ccaccccttt ccaagtctc agtgccctgg tctctcacc tctctgcac 60
caagaacccc aggtctgggt ccggggccca ctctctctc ttcaggtcag atctgttccc 120
ctggaccacg gttctctggt aggtgacctg gaaggccttt gtccccgggg gcggggccgg 180
cacccggcac ggacacctgc aatgtcaccc tcttccacga ggggtgcgcg tagctagcac 240
cactctctag agctgagaga cctttcaaat cctgcttaag agtcccgggc tttctctaca 300
gccttatcag ataagagtca ttaacaggag gtggagctga aggagaaaaa aagccctagt 360
gaaaagaaag aatgcataaa gtagccaaca ctgctgggag ttctagagat taagggaaaa 420
ctttcactac ctgcttctct acttgaattt cataaattac ggtattgttt attttattac 480
tgttttttgg ttttgttttt tagagacagg gtttctttgt gtagctctgg ttgtcatgaa 540
acttgctctg tagaatagct taacctcaaa ctcacagaga tccgcctgcc tctgcctccc 600
aagtgtctgg attaaaggcg tgcaccacca ccgcctggca cttattttac taatttttaa 660

```

WO 2005/005597

PCT/US2003/027106

```

aatttgattt tttataggct agagagataa ctgggtgctt caaagctgcc gttgaggaga 720
acatgggttc gagtatcagc tcacagctgt ttgtaattcg tttcagtga cctgatgctc 780
tctctggtct ccatggactc cagacacaca tgtgatgctc aggcaggcac acatacaggc 840
aaaacatcaa aacgcataaa ataagttttt tttctaatt ttgtaaata gtgtgtgggg 900
attacatgta ggggaaggca tgtgccaca gaagccagaa gaggtgato tatcccttga 960
agctgaatc acagatggtt gtgagctgcc tggcatgggt ggtgggaacc aaactcaggt 1020
cttctgcaag atcaatctgc actctgaact totgaacct ccttctggtc ccttttttat 1080
tttttttatt aaagatttat ttattgtata tgagtacact gtagctgtct tcagacacag 1140
cagaagagga catcggtatc cattacagat ggttgtgagc caccatatgg ttgctgggat 1200
ttgaactcag gacctctggg agaacagttg gtgctcttaa cgttgagcca tctctccagc 1260
ctcccccttt ttattttcaa ccttagatgc catatctttt gagctgtgca cctcgttttg 1320
ttgtcattgt tgtacatatt ttacaacttt gagagactat ctgtgtgtat acatacatgt 1380
gtgcaagtgc acaccaccat gtaggtgtgc ctttgtgcag actagaggtc agcactgggt 1440
gtcttctcgc gttgtgtccc atcttcttct ctgagtcagg gcctcggtat aaggccgaat 1500
cttggtgatt ctgctttggt ggctggccgg ccggcctgcg agctcagaga gcctcctgtc 1560
tccacctcca cagggtctgc attatagttc ccgtgttggc catggaaccc aggcctctgt 1620
gtcctatgtg caggcctgag ccatctccct gaccccggtg tactcccatg tcacaaggag 1680
acgtacacaa aaccgcctg tctccagaaa cccaagtcca gttctgccca ctagggtgctg 1740
agaaagataa cgttgagaag gggatttagg gatttctaata tgccaagctg tgcgtcttct 1800
acctctacg cacagtggg aggagatcgg aaaggagaga tttgggtcca gaggggcatg 1860
caggggtgtg gagctggatt cagacttctt atggtttttg tgttttctc tatgaatcat 1920
ctctgccatt ggcactgaag agcatgccc tcacacact atggtcccat gacctcaggt 1980
aattacttgt agggattaca tggaatctgt gatgcogcta ccattttaat tattgcaatg 2040
tataagcaca gaagcatgtg tgtatgtatg tgtgtgtaca tgtctgtgtg cctgtgtgct 2100
tgtctgtgtc catgtgtgct catatgtgtg tgtccatgtg cacatgagtg tgtgtgtgtg 2160
tgtgtgtacg agcatgtgtg catgtgtctt tgtgcacatg tgtgcacatt tttccatttc 2220
tttttaaaat gtttttaatt taattttttt ttttttatgt tatgaaatcc gcctccttct 2280

```

WO 2005/005597

PCT/US2003/027106

```
gcctcogaag tgctgggato aaaggcgtgc gccaccaccc ctcagagagt cttecatttc 2340
ttaatcagtg ttttcagaat ctgggtctgag gatgtagctc agttgggggtg cttgcctaac 2400
acgtttgagt gctgtattca aacctaggca tcgcgtaaac acagtgtggt ggagaacacc 2460
tgtaattcca ggaggcagaa ggatcagaag tccttgagca gccttggtta ataggagatt 2520
caatgcggcg ctgggcaggc atctctgaac caaaataaac ttgaatttc aggtacaggt 2580
tttccctctc tgagctctta gaactgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg 2640
tgtgtgtcgt aaagggcctc gctttctgat ttgtcttttt taatatattga tgtctcctct 2700
ctctgtgttt ttcaagactg ggtttctctg tgaagccctg gatatcctga actcactctg 2760
tagaccagac tggcttgcta ctcagagatc tgagtgtctc tgctgtctct ccaagtgtct 2820
ggactaaagg cttttgccac cactgcctgg ctagaaatat ttctcaagag ctagagaggc 2880
agctcattag ttaagagcgc ttgctcttgc agaagagcag tgttgggttc ccagctcctc 2940
gaccaggtag ttacatagtg ccaggaaact catctccagg ggatccaacg ccttctctctg 3000
gcctcagtggt gcacttgcat tttccttgta cacatattac taaataaaaa gaaatcttta 3060
gaaaaataaa ataaacaaca cagctgagta acttaaatca ttccatgggc tcccggtctg 3120
tggtgcccc ttctgcctca ctaaggtcgc atctttggag ttaaaatcag tatagagctg 3180
atgtttctct taatcttcag acaccacagt cactctgagc tccagttcca ggggtttgat 3240
gcccctctct agtctctaa ggcactacac actcgtagtg aacatacata catacatact 3300
tgcaggcaaa acattcgtac tcattaaatt ttttttaaag 3340
```

<210> 12

<211> 3933

<212> DNA

<213> Mus musculus

<400> 12

```
gtctctcccc tcgggtctct aggcatacag cttcccgggc caaaggcaga actctgccct 60
tggcaagctc tgccttacct gtaccaagat caccagctct tccgttctct tcagggaacc 120
ggcatctgag actcagctgt atgactagag gacatttctc cttagccttt ctttccacag 180
gcatacgggc gtgctcctca cactgggtgt ggcgaggcat ggggcttctc cacagtgggtg 240
gggtcggagt ggcttgtgtg cctcgggtggg tttgtgagct ggggtggaacc tgaccccgaga 300
gcctggtagg gtctgtctga gcggtgaggg tgtgtgaggg atggtgacta gcccggtgcc 360
```



WO 2005/005597

PCT/US2003/027106

cactttctacc cctacctgct ctgccctcat cgtccctggc actgctggtg ggccctaccc	420
tgtccactgt gtctctccat gagtcctaag tctctgtga gccggctggt ccgtgtgcac	480
ctgtgtgcac gtgtgtgtgc gagggggcaca ggagtcctgt cttgtctctg tgctgtgtgg	540
gcagatggag gttggcctgt ttttactctc tctgtgttcc tccttgtctt tttttattcc	600
ctctcatctc catcgactc tgccatcaac ccaactctc atctctcaga tcagcgagaa	660
ggttggttgt tttcactctt tatccatcta cagttcgccc acgactgtg ccgcgcagtt	720
gggaccagcg ggcctggtcg gctccctcag gctcgtcca gccggcctg ccgcgcagtt	780
ggcctcttct cgggtgttgg gctggctggc aggcaggacc agggatgggt gggcaggcct	840
tctgcctctg atgtacctgt tgtttgacct tgattcgtg tgtgtctgca tgtcccttta	900
gccaggctcc gctgttgag tgccacaca tgcacggtg acggcataaa actgtacctt	960
acagaactcg actcagcttt gcaccagac caggctagcc ctctgtttca ggaattggtca	1020
tggggatctc tgtcagagaa actaaactac atgcttgcca tgtaggagtt cagggaagct	1080
tctaccattt cccaccacc ccttatgttg tctcggaac taagagaagg cagaactgca	1140
ggaggcaata ggaggaggct aatttagagt gagggtgcc cttgagatct cacagtacgc	1200
gacacagtc tgcatgtct gccctgccct tgaggccccc agagccttac caatgtcca	1260
caaagcagac tggctgtact gagacttaag accagccttg gtctgcctct caaagacct	1320
gatggcgtg gtccaaggca ggtggcatca ttttcataca ctgagtaagt gtcccgacat	1380
tatatctttt ctgtctccta cggggtccaa accaaggta cctctgcctg ccagaccact	1440
ctaccgcgag ttccaaggca gcctctgtg ctctcagagg gtacagtgtg tgtggctcac	1500
tgaaccagta acagccctca gtccatgct gggcagtggt actgagcgtt cagatccagt	1560
ttgcttatgc ctggagtgc tgaattgtca ctgcagtcct cttaggcctt gagtatcaat	1620
cagtcacgct cagccttaga ttgggcaggg ctttttgaac ctccctggat cctctccag	1680
agctgtcccc tggagccagg cctctatttc ccagtcacgg accaacaagg ggcgtggtgt	1740
cctttatata tcgtgtggtg taaagggta atcactgggc tttgggggtt ccaaggaaga	1800
agcacagggc agaccaccag taccaggtgg cctctgcac atgctctgtg gctttgagtt	1860
tactccggga ggacaaggga gccagtcagg aggagggctg cagcctgggc tcagatatca	1920
acataagcct ccactctgat gcactcctga gctctggggc atttcgggta caccatttcg	1980

WO 2005/005597

PCT/US2003/027106

ctgaccagcgc	ggatctgcc	gggogttcag	aaaatagtc	tcagcagaca	gccagccgc	2040
cagccactcc	ccccacccc	cttcacctac	cctctgcac	ctttgtctc	ccccaccca	2100
ccctgtggc	ccacaaaaa	tacacacata	cacaaatatt	taacgggaag	gagaaatgag	2160
tttctaaata	ttcgggggg	atttgccggg	ctggttaatt	gtttggtgct	gataattgca	2220
tottacattt	ttctagcttt	acttaaaact	gtgtgccggg	tgtgccagca	tttaattact	2280
gctctgggc	agccacaag	ttatttatta	aagagttatt	ttatcttgat	acagtggatc	2340
ctgcccctta	tcccctcct	aatgttgtgt	tattttcatc	agagaaattt	ccgcaagtga	2400
atgcagattg	cggggctacc	tcccctcg	attaggctgt	cactccactg	aatgcgggata	2460
cctccaggcg	cgcacccacc	ctattatagg	gggtgtgcag	cgcaataat	tagacttaaa	2520
agttacagct	gaaatataat	ccagaaatgg	cagggccctg	ttttggaat	tgctataaa	2580
atgtcagcag	taaggatgca	cggggaacag	taatagaccg	gcattgttgg	agcctgagat	2640
tagaccctaa	gtgcattttc	cccagctcca	gtttttcctt	ccctgctgtt	gctctgtca	2700
atagaccaag	tccagggaga	gtcctgttcc	ctttggaggc	ccctgtgctg	tgggcgccgg	2760
gggaggacgg	tggagatgct	atgttggagc	atcagccact	tgcaactgtt	ggcacaggag	2820
tagctgtcta	ggctgggcta	ggacacaggg	cctctagcat	ttggggcact	ttgttgccct	2880
tttcccattt	ttcagtagat	atgttggcct	acctgagctc	tagcagattg	acttccagga	2940
gtctttgcat	gtggctggac	cccagtgccc	ttctatagga	atgtagtatt	cagtgggaata	3000
cctggggcct	ctggctgagt	tcctttccca	gtgtgagggt	gacctgacc	tcacacctgt	3060
ctgtagcccc	caaagttctc	cctatagctt	gcattctgga	gggaaaaata	aagccattct	3120
tagccggggc	tggtgggcaca	cgcctttaat	cccagcactc	aggaggcaaa	ggcaggggga	3180
tttctgagtt	caggcccgac	ctggtctaca	aagtgagttc	caggacagcc	agggtatata	3240
agagaaacco	tgtctcgaaa	aacaaaaaaa	aaagaaaag	ccattcttag	tgctacttcc	3300
catggggggc	cagtttctgt	acatcgacta	gagatggagc	ctttgaaagg	agcggcccg	3360
ggcattggcc	tggctccgaa	gctgatccct	gaggactctg	ctggcttgga	aaacactgtc	3420
caccatggac	tatccagggg	tcaaagtttg	gacatgttta	ggtatgggcc	ccaggtattt	3480
tagccaaaga	cctaacttct	actgcataaa	cccagtggcc	cctctttcat	ttgggttcca	3540
ccattaacta	gagccaccat	taactagtgt	cactctcaaa	agtcttatct	gtatgccatc	3600

WO 2005/005597

PCT/US2003/027106

```

tggagctcga cattatgcc acgctaaagc cccatggcct tcatgggctt togaagatag 3660
agttttttacc acacagacct gatcttccctg aggatataaa ggcagatgcy tcacttccctg 3720
tgtcagcatt gactctggcc ctcactctgca attgagacat ggtggcacag gcaacctctg 3780
tacagagtac agagtggcct tccactaggc atgatgtgca tggctttaat cccagcactc 3840
agaaggcaga ggcaggtaga cctttgtgag tccaaggcca cctgggtgta tacactaagc 3900
ttcaggatag ccagggatata ataaacctg tcc 3933

```

```

<210> 13
<211> 2272
<212> DNA
<213> Mus musculus

```

```

<400> 13
gatagatgat agatagatag atagatagat agatagatag attagataga tataaagtgg 60
aaatagaagt tccaagtcca ctgtgaggag ccagggatgg cactgttcca tgtaagtgtt 120
ccttgagac atttgatctc tacagttgtc tggcctggcc ctcttagact gcactgtcca 180
ataaaactat tgtagaactg tttaaatcca atttgaaatt tcaaatagcc acataaaaat 240
gtaaaagaag ataaagttag aggttagagt caagtttagc atttataata ctctgggttc 300
tatcaccagc acagactatc agatgataaa tgatagatga tagatgatag atagatagat 360
agatagatag atagatagat agatagatag atagatatc attccttttt agtaagtcca 420
aatagtcttt gaacatgtaa tccacataaa gctaattaca aaataaatat attacatgga 480
tttttatatc atgtctttaa agttttatct gttgtgcata ttttaattca gatcagtcac 540
aagttagctc catattggac agtggagcct tacaagactg acccttcccg ctgccttcca 600
aaacatgttc acatttagag gatggactct gccaacactg cctaagcccc ttcattttac 660
aggtgaagat gaccagatct agagatgctg ggttgcttag aatcccatag ccattcacat 720
cagaagcccc acccttttgt ctgacttcaa ttgctttcat cattctttct ttccttagat 780
ttgtgttctt gcaactactc actgtgagac tgttgctgtt gggttaaatat tgagccagga 840
gtcttaaaaa catttggtcc actcagtaaa gccactgttt gatttggtgg aaactgtttt 900
gagcagagta ggtagaacta ccaggcacat tgacagtctc ccatgagata gtaataggag 960
gtgataatgg ggacaggggt gactttatgc ttgttggtgt tgctgtgggc attataggag 1020

```

WO 2005/005597

PCT/US2003/027106

tatgtgactt caaattttga aatgctagct gcctgcttac aggaaggag atgagctgtt	1080
cccatgcaaa gtttattgtc tagttgtatg tataagccta cacatgatga atatcttaat	1140
gcttaactct ctctggaagt ggcagggtta agcttttata ttccatattt ttttcttgta	1200
ttaggaaagt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtat	1260
gtgtgtgtgt gtgaatgtac tcctatttct cactcagtta tacttaaagt gtgatgattt	1320
ttgacaagtt aatcccagta cactcctggc atgtaaagta ttttcagaat gtaagcccat	1380
gtggaatttc gttggcttgg tatgacgggt tcgggcaggg gaggcatagt gtgatcccg	1440
ggagtgttgc gagctgcca gtatttgctt tcgggtgtga aagcgtgctt gacgggtgga	1500
cttctctagc tggaaggctc tttgttcac cttcctaaaa catttatcag cacgggatgt	1560
gtagatcggt taagagagtc ccttttattc atgtgactta gttcagtgat cttagattta	1620
gagttaagtt tttgtgttcc agggttggga ctaattccca gccatggccc agctttacc	1680
acaaaggaa caccgacctg taaggatatt catttgatgc gtttgctttt gttcctgggt	1740
ccagtcattg gattttgcct atagtgcctt atgtggctat acttagaagt tttatagctt	1800
gtagcaatca ggtgaaagta cagggatatg gctgagtact gtaacttcgc tctgtaatcc	1860
cagccagagg caggaggatc accagtcacg ggcaatttga gctacagagg caaactgaaa	1920
aaggaaaaga aaaaaaaaa gagattcctt tatttccttt ggccttcata cacaatatt	1980
taaattctta atgtacgggt ttaagtcagc ccctacctc cccaccttg gtatgttgca	2040
tagtacacat tagcatttga aacaaaagtt ttgagctata agatgctcat gggagtcatt	2100
ctgaaatatg ttttaagggtg attgattcgg aaaggatgca aatccaagtt aggtcggtg	2160
aggcctcccc gcttctttag aggggtgata ggaaggtttg aggaccaggt ctgcttcggt	2220
cggagtgtgg acagccagtg agggcagtg agcaaaaccg tgtctcagaa tc	2272

&lt;210&gt; 14

&lt;211&gt; 1554

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 14

atgtatgtac acacatatgt gtatatgtgt gtgtatgtgt gtatatatat gtacatatat	60
atgtgtgtgt atgtgtatat atgtatacat acacacacaa acacatatat atatatcaca	120
gaaagtatat gaccatttta aaatatcact atttgcattt gatttagttt tacacaatac	180

WO 2005/005597

PCT/US2003/027106

tattctccag taacgtttct tctttttcca tttctttcat ttcttttctc tcttctttta	240
ctaaattggc acacttggtt acttctcagg ttttgcaaac atccttaata tggttggtatg	300
gcaaattgcat ttcaattcaa atagcaactg caagttgata tgcagaagaa cagaagtaat	360
gtggtctgga attaatgttc tcaattgctt acaagcaata tgctatgtat gaaaagatta	420
ccaaattaca ggtattaaat tctaaatgat ttaacagttt attatgattt attctattta	480
acaacctagg gagtttgaag ccattggaaa ctccagtggc aagttcaggt goagttggga	540
gttcaggaat ctcaatggag ctattagtgt agcagacttg tgggtaaaat atatgcattc	600
ctcaatagca aatgtgaaag actctctaaa atggacctca gtgacttcatt tctccacaag	660
ctgtctctggc ccactcagca tatcctttat tgttccatga tattaaggca tgtctgcttt	720
tttttttttt taataataaa tccatgacca cctgaagggt ttaacttggt atgcaaggca	780
ttaaggcttt cacagccacc atagggtattt tctctcccat ccattatggt attataaact	840
attactttga tgcocatgga actttcttag tttttcttac acattctggg acactggcag	900
aaataacttc ttccagatta tagttgcttt gtgcaacagg aaggagatca gtcaacaatg	960
gatttataaa ctctcagata acacagaaag ttacatctca tgtccaaaaa tgaccttatt	1020
acttgccctt aatttagttt tgcattgaatt tttaaagcag gaatcataaa tggcccaagt	1080
gtcttaattc aaattcttac ctgactgtgg agaagaaatc attgtgattt ttgaacacac	1140
ataattatgg tttaaaaaca aactaacctg aatttggttg aatatagttt ttcaactttc	1200
tctgatacta ataaactcat cagccagttg gaaattgctt tccagaaaaa attctcattg	1260
cttatatggt catatatgtt tacatgtata aaagatttca aaaacttgga ataagtttag	1320
accattctta ataaggatat taatggatat ttaaagtgcc tgtcttttca gtgtttggaa	1380
atattatttag tgtttcttca gggcgatatc aatcaataaa atgtccattg ctgtgatgac	1440
taggaagatg ttctcttatt ttctttctct tctgtcataa cctgtcttat tcagaactaa	1500
atttcaaatg tgaacagttt tagctgaacc actgaattaa aataattatg aact	1554

&lt;210&gt; 15

&lt;211&gt; 4007

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

WO 2005/005597

PCT/US2003/027106

```

<400> 15
tggtgtgtgtg tgtgtacatg tgagttcagg ggcacatgga agccagaagg aggtgtgaga      60
agctccacat tggctctctc caagagcagg agatgctgtt taccactaag ccactctctc      120
gtccccagga agtgacaatc ttcaggcagt ttgtctgcat ttatacttt ctatttaatt      180
ataatattaa aattttgaag cacacactga gaaatctaaa ggtggtttat tctttccca      240
tttttttaaa gagagtcaaa taaaggttca ttctctcaga ggaggtcagg tgaatacaaa      300
gggcttattg tcaactcaaga gattcttccc aagaaaagtc acattaagaa aggaaaggag      360
agagacatgt aggtcaaaa agagataatg aagtcaagca aagataaatg tgacttaaat      420
aggcatttaa tgtggctgaa tcatatttaa ccatgtgttc tggacatata cccaaagggt      480
gagtcogggt gatatcaco ttaggtctaa ggggaggaag gagcattctg attgagaagt      540
gttcatcact ttctctctgg gactaaggcc ttctccataa tgatggttta attcaatctc      600
gtcaattacc tcttctcaga gagctgcagg ttgtgccacc ttgctggaaa tgggtcaaat      660
ccattaaact tctgttcttt gtgacagagg gaaaaggaaa gatccagcga ttcaattaag      720
acataaatga ccagggtgct gtggcacaga atcagctttt ctggtctgac caagaaaacc      780
caatttccat ctggctagg aagctatgtg agccctcact cacctttgct gttagcttcc      840
tggccatggt taaaggctca gactgcacag gaacacacaa gagttttctt tgtattcaca      900
gtggaagagc cccctcccc acggagttgg gtggagtggc cagaagacct tctccatccc      960
tgccctttgc tgccttgttt ccagaaagga ggggagggaa attaccagggt tatgagatgc      1020
tgctctttgg gaacaaggaa attaatgcag cgacctgaat tatgtgcgtg acacatttgc      1080
atatcgctca ctgacgattt ctgaagaaac aacaaatttt gtgtaattct aatctctttt      1140
gcaaagcaag ggaagaggaa aagctacctc cgatttactg tctacaaaga aagctgaatt      1200
ttaggatcaa atttgcacac atttagtggt aggctaaatg ttaaaacata aggtgcatc      1260
ttttaaatca ctctttgtgt gtggctgagt gtaaatgtca ggcattgtga catgcatggg      1320
tgcatgtgtg catgggtacg tgtatgcatg catgcttggtg tacgtgtgtg cttgtgtgog      1380
tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgcacatg tatgcatgtg      1440
gaggacagag ttcaatgaca ggtctcatc tctatcatta tcaatgataa tttatagctt      1500
gaatatcttg tatcattata cctatgtctc ccagatcatt atattcattt gggggggtat      1560
ctagtataat ttactattat tatggtaatc atggaatttg ggggatggaa tgactgattc      1620

```

WO 2005/005597

PCT/US2003/027106

```

attgtcagtt tataaccagg ctgatgtaga aaactcaaat gaagaccaat tatcaatgtc 1680
ttttagtgca ataaaaattaa tatctggaga agtgagtccc tctaaggaaa atcttctagt 1740
cagagaaggc ataggaaggg agaatgctta aagtttgat caacttctct ttgtgaggtt 1800
taagcaattc tcatgttgca atcgccaggt atcactgtaa tcctcgagat ttctagaaga 1860
gcaaatgggt gaagcttgca agccttttct gaaataagga aaattggcat agtttagaaa 1920
aaaaaatgt tgggagattt cttacaatt gctttttgct gaacaaaagg ctggactttt 1980
ccttgatcaa gttgcagaaa tgetgtctgc tctgtgagtt ttgtagagag aaaaattaca 2040
cattttataa acctggcttg gctgcttttc tgttttgatt ttgacttctg attctgctct 2100
gattcgactt agctaccaa gttgacagat tattgaccca cagtccacgc ttataccttc 2160
tgtctctccc tccgtcccta gaagtctctg tctcttcaat cctccatca cagtgttaat 2220
ggtgatatcc agatgacttt gaccacaaga gaggcacaca gggtagagct gacatcatta 2280
accattcaat tcctcccctc tcatttgagt tttcttatca gataaaggtt gctagtgttg 2340
aagtcatagt ttccaaagaa acaaggcttg gggatgctcc aggtactaca ttcagagctg 2400
ggggggctag atttggaaac tgccaagtat tttagagcca gaagcacaca tcttttctct 2460
tcgtgaagat gctgtgtcca gcaagaataa tgacaacaca caagccatgg actcagtagc 2520
actgaagtgt ggttcgaagt gggtctcatg tattatttaa ttgttagtct gaccttcaga 2580
ctagaacctt ggagctataa caaggataat gtatttaagt aaccagctg gtaagtggtta 2640
aagcatggac tgaccacaga ttctatctc tcgggaccag aagttaatc agagaggtta 2700
atcgatcaaa ccaagaaaa ttacgcttta agttaaatta agcattctaa aattatctag 2760
taatctcatc tctgcttctc gacacatgtc agatttgtat tggtagctctc aaaattaatt 2820
taccatatgt ttgtgtctct tgtgctagac tttagagcaa ctgttagaga tcaataaaca 2880
agctctgaca catttcatac tctcatgaag ttctgccttg gagaatctcc ctagttagag 2940
tttctcaggt taaaattctt ttcaagaatt aattaaatta ctctactgag ttttagttcc 3000
tgtctctctg cttgcagatt catatgggga cccatttcat cattatattg atttagatcc 3060
ttgccattca aaacgcttgg catccattgt cagccatact acagaaacag agatgcacce 3120
ttgtatagtg tgcagcgcac attccctcaa aatatttact atgtagttct ctatacgtta 3180
ggaaatctat tcattcaaca cagatgttga gcctcattta atttacttcc tccactttac 3240

```

WO 2005/005597

PCT/US2003/027106

tgtatttttc ccagtatatt tttgccccgt ggtttttatg ttagaagaag ggccaacaga	3300
aagatagcag tgagttgggt aacaagtgtt tctttttgca aagtaaaaga cgccgttgct	3360
gggaagcag taagcgtgaa caggaggagc tgtctaatag actgacgcag ttggtgatga	3420
cgtcagcact gggcactgac ttaacagaac tccactggga ctgtctatc ttctgtttgt	3480
ccagtttgca gctaactcct agcaatgtcc tcagaccaca ggagaagggc taaattgctg	3540
attaaaatc cttaaagaac aaaataactt caactgtatc ttcttgatt ttggttttta	3600
gttcctagac actgtaaaat gacacacaca ggtgctgctt acctgctgct gtggcatcaa	3660
tattgataaa gaaatgtact gcaaagtgtt tcattccatac ccagagcagg tgctagagca	3720
attcattgta tatcatataa gatttagatc ttaatccttt tttttttcag atatacgtgc	3780
atacacacac agatacagac acacacagag aaagacacac agacagagtg gcgcgcacac	3840
acaaacaaat gctgtgctat ttgtatgtat aaccaacctg ggtagtatct gtgtactgtg	3900
aaccctctgt ggttgggtt tagccatcag agacgagcca tcagagoccca gcctgatggt	3960
agagocccagc tcctgtatct ctggctgag cagttctttt tccagct	4007

<210> 16

<211> 2755

<212> DNA

<213> Mus musculus

<400> 16

gaacgatagg gccaaaaagt gggagtgggt gggtagggga gcagggcagg ggggagggtg	60
taggggactt tcaggatagc atttgaaatg taaatgaaga aaatatctaa taaaaaattg	120
aaaaaaaaag tctgtttcca taccctaaag atattcaaat atctgatata aagtctctaa	180
ggagagtaaa tagagcctct tatcaaaatc tagcatttgc cattcacttg agtaagatat	240
gcaagatgaa gttttaccag accttttgtt gacagaactt ttctggggga tacacaatac	300
acatatctac tcaccagacag agggatcca tgactgacca cagtacagat accaccgaag	360
tccaacttgg taatccaag aattttatta cgattactta cgggcgtatg gatgaggagt	420
tacttaaaagt agcagaaaag actgagaaga ctgtgtcacc aaagcccacc acagcatagg	480
ggatgactta caaagctggg aaccaggagc acactacaca gtctgcaggc agctcaacca	540
gttggggatt gtccttgcca ggtgcctcag ttggtctaaa ccttttccag gcagttggct	600



WO 2005/005597

PCT/US2003/027106

tgggctcagt cttctctgca gcttggtttc tctgagagtt gacacagctc aacttccttc	660
tgctctgagag agactttcag ctttttacaa ttcaaatggt atcccccttc ctagtttccc	720
ctctgaaaat cccctgtcct cctcctcctc tctgtgtctc ccaacccacc cactcctgct	780
tcctggcctt ggcattcccc tataccaggg catagaaatg tcacaggatc aagggtctct	840
cctctcaatg atgacctact aggccatcct ctgtctacata tgcaattaga gccttgagtc	900
cctccatgtg atttctttga ttgggtggtt agtcccaggg aactctgggg ttgttggtta	960
gttcatattg ttgtctctcc tagggggcta cagaccctt cagctccttc attggggacc	1020
ctgtgtctca tctaattgat gactgtgagc atccacttct gtgttcatca ggcgtggcca	1080
gagcctctca agagacagtt atatcaggct cctgtcagca agctcttggt ggcctgtgca	1140
atagtgtctg ggtttgtgtg ttgtttatgg gatggatctc cagaaggggac agtttttgga	1200
tgggcattac tttagtttct gctccaaatg ttgtctctaa taactcagggt attttgttct	1260
cctttctaag aaggatcaaa gtatccacac ttgtgtcttc cttctcttg agtttcatgt	1320
gttttacaaa ttgtatcttg ggtattctga gattctcggc taatatccac ttatcagtga	1380
gtgtatatca tgtgtgttct tttgtgattg ggttacctca ctcaagatga tatcctccag	1440
atccatccat ttgtctaaga atttcatgaa ttcattgttt ttaatatgctg agtagtactc	1500
cattgtgtaa atgtaccacg ttttctttac ccattctctc gttgagggac atctgggttc	1560
tttccagctt ctggctatta taaataaggc tctctatgagc atagtggagc atgtgtcctt	1620
cttaccgggt ggaacatctt ctggatatat gccacaggaga ggtattgcag gatcctctgg	1680
tggtactata tccaattttc tgagggaacca cctgactgat ttccagagtg gttgtacaa	1740
cttgcaatcc catcagcaat ggaggagtgt tcctctttct ctacatcctc accagcatct	1800
gctgtgcctt gagtttttta tcttagccat tctgacttgt gtgagatgga atctcagggt	1860
tgttttgatt tgcatttccc tgatgattaa ggaatgtgaa cttttttttt tttttttagg	1920
tgcttctcag ccatttggtt tttctcagtt gagaattctt tgtttagctc ttaccccact	1980
tttaaatagg gttatttggt tttctggagt ccaacttctt gagtctctc tctatatatt	2040
ggatattagc ccccttttgg atttaggatt ggtaatgagc ttttcccaat ctgttggttg	2100
ccattttgtc ttattgacag tgccttttgc cttatagaag ctttgtaatt ttatggcatc	2160
ccatttggtg attcttgatc ttacagcaca agccattgct gttctgttca ggaatttttc	2220

WO 2005/005597

PCT/US2003/027106

tctgtgtgcc atattcttga ggctcttctc cactttctcc tctgtaagtt teggtgtcgc	2280
cagcaetgct ttgtcttact ctgtcaggga cgggttgaat caatctggtc cgtttcagag	2340
agtttctgat gctgttttaa tatggacaaa actgtttacat aaaacacttt tagtcaaac	2400
ttcacatgtg ataccaacca gggtcacatt tgttaacctc cagagagatg aacaagtac	2460
actcagaaaa cctctctcag attcccaacc taattactct caaacagaaa tactactttt	2520
gtttttgttt ttcagataga gtgtctctat aaagccctgg ttactctaga aatggcttat	2580
gtagaccaga ttggccttga atccatcaag atccactac ctctgttttc tgagtgtgg	2640
attaaaggca tgtaccacca tgccagggtta aaaaaacca cacatacaaa aataatacaa	2700
aactaatcaa ccaacaaccc aacaaaaaa caaacaacaa aacaaccccc aaacc	2755

<210> 17

<211> 1811

<212> DNA

<213> Mus musculus

<400> 17

ttttacatgt acctagagaa agaaaaacaa aaaacaaaaa aaccaaaggc tcttaccatg	60
ttgagtgtct gactgaaagt gtgcccctgg gactccatgt gtaacagtag caatgggatt	120
gcagcaataa agatgggaga agacactcag gtatggctgc attgaggaaa ctaatcatat	180
ccagcatttc ttggtgtgaa ttaaaactgac atgggtgaaag tcaagctttg gttttgtaaa	240
tgccagagaa aaaacagaga acattgcaca gtaaacctga gtttaaatgg cctcagtgtt	300
tgaggcaagc tttgaagcta ggggtgtcaat atctgtgttt tctgtaacta atctgaagag	360
ccctcgagag tactgtgtct gtgaggcctg aagttcagat ttctctccag agttcttttg	420
attgttctta tgtaccaggc agaagtcatt gtgattctta gaatggatca tttgagtgat	480
tactgtcctc ctgggtggct acaaaacaca tgggtccaaa agaatttcag gggtaagacc	540
tttoggcttt agaacatcca catgtggcag ggcacattgg cctttctta ccagaactc	600
ttttgtgtgg ctgcattctt ttctccagtt ctctcttaac tggagcatgc ctattctttg	660
tccttttgtc tttagtatct ttgttgttgt tagatgccat ctgaagttac actcacaagt	720
ttaaagcaat gctgccttct tgtcagcctt gtgattctgt gtgcatttca tgcaggggaa	780
cctgtatgtt tgctctctgc attcttacct ttcatattgt ctctctctcc accacatggg	840
aaatgttatg agtacacatt tgtcttcctc aacgaaaatg catgtgaaaa cctctctgtc	900

WO 2005/005597

PCT/US2003/027106

```

cttcttgcac cttagctttg tttgtttctc acatttttac tgatattcca caagaaagat   960
ttgccatata catttaggaa acattgagcg atagatagtt ctccagaaa ttctcaaaga  1020
catgttattt accatatcaa actctcagga atgtattgga aaattatcct agtaacattg  1080
ctgttactta tacctgtgcg tggaggaaaa aagttttatc atgacacatt tacctttgat  1140
cataaataaa agagaaaggg ccaccttttt ggagttagtc atggtagtca ttagtgatat  1200
ttttgaaccg tttttaattt gaaatacttc aaaggaaagta aaggctcatgg cttagctcaa  1260
aaaaatgctc cagaagttgg gctgcttaaa tcacagtagc aataatatac tgtgtgtgcg  1320
tgcatgctgt tgtgtgtgtg tgtgtgtgca tgcgtgtgtg tgtgtgtgtg tgtgtgtgtg  1380
tgtgtgtgtg tatgaaatga gaattgccac ataattggag catttgcatt catccgcaa  1440
tcattgttag acaactgta gctggcgcgc ttgattaaag ccaagtgctc cctgtggctg  1500
tgaggaaagag tttttcttgc aaaaactttg gcaagtgatg acttcgaaac ttacaaaggc  1560
tattgccttt ttttttttta acaccagtag tgaccttcag ttccctcagt ctgagttaa  1620
gggtagaatt ctaaatattg attctaactc gtcttttgtg gaaaattttg aaaatagtat  1680
gtatatgtaa tattgtatat gcaaatgtg tttgtttact tgttttgcat atgaccagca  1740
ctgactgaaa ggcatgttta actataaaca ctgttgcttt ctttgtgaaa tgaaaaataa  1800
agtatttaaa t                                     1811

```

```

<210> 18
<211> 2438
<212> DNA
<213> Mus musculus

```

```

<400> 18
gcacgctttg tgtgtgtgtg tgtgtgtgat gtgtgtgtac atgcgcgcac gtgcatttgt   60
gtgtgtgtgt gtatgtgtgt gtatttgtgc ttacacatgt gcaagtgaaa gtatgtgtat  120
atatgaatgt aagtgtgcat gtgtatgtgt gtgcattgtg gtaagtatgt gtgttaattg  180
tgttttttgt gagcaagtaa ataaaaaat agttctttct taaagcagca aaagaaaagc  240
agcaagtcac gtaaaaaata gtcccatcag aataacagca gatttatcag tagttatcct  300
acagacaagc ggaggatggc attatatact caaagctgta aaaaaataatt tttcaatcaa  360
aatataccta gaaaagctat ccccaagga tgaaagagaa gtgaaaactt tcctaaagaa  420

```

WO 2005/005597

PCT/US2003/027106

aacaaaaact caagacattt gtcagcattt tatcagctct acaagagatg cccaagggag	480
cagtttatag aaattgaagg atgactacca atatacaaat gcacaaaact acaaaaaaat	540
gtgcaaaata gtgtcaaaat atgcaggtga atgaggaatc taactctatt tgtacaaga	600
aatcaccaag gcacaaaatg aacaagaaag gtgggaacaa aaaaaggata cacaaaacca	660
gaaaaaatg acagtactga ctattcattg ttaataatgt taaatattgc actggcagtt	720
cttctctttt ttttttattt tattagatag tttctccaat tacatttcaa atgttatccc	780
ctttctgggt ttccccctg aaaatccctt tcccttaact ccttccctct cccctgctc	840
accaaccac ccactccaac ttctgtctcc tagcattccc ctacactgga gcattggagcc	900
ttcacaggat gaagggcctc tctctccatt gataaccaac taggccatcc tctgtctcat	960
atgtagctgg agccatgagc cccaccatgt gtattctttg ttgtgtggtt tagtccctgg	1020
gagctctgtg gatagtgcct agttcatatt gttgttctc ctatggagct gtaaacccct	1080
tcaactcctt tgggtccttc tccagctcct tcaatgggga cctgtctac agtccaatgg	1140
atggctgtga acatccactt ctgtatttgt caggcactgg caaagcctct caggggaaag	1200
ctatatcagg ctctgccag caagcacttg ttggcagcta caatagtgtc tgggtttgga	1260
tggatcccca ggtggcacag tctctggatg gtcattcttt cagtctctgc tccccattt	1320
gtctctgtaa ctccctccat ggggtattttg ttccacttc taggaaggat cgaagtatcc	1380
acactttggt ctctctctct cttagatttc atgtggtttg tgaattgtat cttgggtatt	1440
tcgagcttct ggctagtatc cacttatcag taagtgtgta tcatgtgtgt tcttttgtga	1500
ttgggttacc tcactcagga tgatatctc cagatcaatc catttgccca ggaatttcac	1560
aaattcattg tttttaataa taaagtggta ctccattgtg taaatgtacc atattttttt	1620
tttatccatt cctctattga ggggcactcg ggttctttcc agcttctggc tattataaat	1680
aaggctgcta taaacatagt ggagcatgtg tccttattac ctgttgagga atcttttgga	1740
tatatgccca ggaatgggat ggctgggtcc tcaggtagta ctatgtccaa tcttctgagg	1800
aaccgccaga ctgatttcca aagtgggtgt accagcttgc aacccccacca gcaattggagg	1860
agtgttctcc tttctccaca tctcaccag catctgctgt cattggagtt ttttatctta	1920
gccattctga ctgggtgtgag gtggaatctc aggggtgttt tgatttgcat ttccctgggtg	1980
actaagggat ttaaacactt tttaggtgct tctcagtcac tcagtattcc ttagtgtgaa	2040

WO 2005/005597

PCT/US2003/027106

gttctttgtt tagctctgta cccccatttt ttaatatggt tttttgtttt tctggagtct	2100
aactctttga ggtctttgta tatattggat attagccctc tattggattt aggattggta	2160
aagagatatg agcacagggg gaaaattcct gaccagagca ccaatggcct gtgctgtaag	2220
atcaagaatt gacaaatggg acctcataaa attgcaaacc ttctgtaag caaaggacac	2280
tgtaataat accaaaaggc agttcttatt tctttttctg gttttttttt gaggcagcag	2340
agggagaaga gtgtcagcga gggtaatttt tggtcttagg agatatttag ggttgctgta	2400
taaagcatct tcttgatta agtctaagtc gatttagc	2438
 <210> 19	
<211> 1712	
<212> DNA	
<213> Mus musculus	
 <400> 19	
ggcagacggg agtttctcct cgggacggag caggaggcac gcggagtgag gccacgcattg	60
agccgaagct aaccccccac ccagccgca aagagtctac atgtctaggg tctagacatg	120
ttcagctttg tggacctccg gctcctgctc ctcttagggg ccactgccct cctgacgcatt	180
ggccaagaag acatccctga agtcagctgc atacacaatg gcctaagggg cccaatggt	240
gagacgtgga aaccgcagggt atgcttgatc tgtatctgcc acaatggcac ggctgtgtgc	300
gatgacgtgc aatgcaatga agaactggac tgtcccaacc cccaaagacg ggaggcgag	360
tgctgtgctt tctgcccgga agaatacgta tcaccaaact cagaagatgt aggagtcgag	420
ggaccaaggg gagaccctgg cccccaaggc ccaaggggac ccgttgggcc cctcggtgaa	480
cctggcgagc ctggcggttc aggtccaatg ggtcccccag gtccccctgg cctcctgggc	540
aagaatggag atgatgggga agctggggcaa gcccgggcgt cctggtcccc ctgggcccc	600
cggacccccct ggccctggag gaaactttgc ttcccagatg tctatggctt atgatgaaa	660
atcagctgga gtttcctgct ctggcccatg gggctcctct ggtcctctgt gtctccctgg	720
ccccctggtg gcacctggtc cacaagggtt ccaaggcccc cctggtgaac caggaaacacc	780
aggaggagga ggagaagaaa taatgagtga ttgtgtctcc gttttggaaa agagtttgat	840
gggttactaa tgttggtgaaa tataatatcc aaacatgaaa ttctaataaa ataagtgaaa	900
gatatcagaa agccttcaaa atcctgcaaa cacaatatcc agaatatata ttaaatttaa	960
ttgacaacta taccttctta gatctattgt tcatttgata attatttcaa atttttctct	1020

WO 2005/005597

PCT/US2003/027106

```

ctccatttaa tagtatggct cttaaagagac ctgcagtgtg tgtaagact atttggattt 1080
gtgctttcat aaggcttaaa atgtttatgt attttttttt aattttctat ttgtatcttt 1140
gtatagcatc tttaagaaa tgtgtactca aagaattact catgtagaat ctcactgtgc 1200
tgccatctgg gacatcaagt tcatttgtga acccatgctt cctctcagca tcataagaag 1260
atcactacag aagctgatca ccacacttaa ctagtgggtat tgtaaaatct cttcattaat 1320
gactttcatt ttgtcttggc ttgtgtataa aattgaattg aaagtttata ttatctcatt 1380
tgctaacagg ttgtcttaaa accctcttag aaataacatt tttattactt gtcagtgttt 1440
tttttattta cagcaagata tttaaacact gaatatattt tgtagtattt aatttttcat 1500
tattttaaac aatgtttaaa tcaaatattc aattatatta tgccattcct ccaagttcct 1560
catattgtct cccattttct acccaacttt aagttctttg tcaataaaga tacaataatc 1620
caattgaaaa caaacccctc aaaatcagga aaacacattc aaacaaaacg atcagaaaaac 1680
cccaaaaaaa caataaagaa aacaacaaaa at 1712

```

<210> 20

<211> 3651

<212> DNA

<213> Mus musculus

<400> 20

```

aaaagactgg ctagtgtaga atgcaccagg ggatgaggtt ccagtgtgcc attctttaac 60
aggttttgcc actgcotttg actttttata taatctatta ggtaatcagc gtaaacaaaa 120
atacctagaa aaaatttggg ttgttactga ggaaatgtat gaatattcca agattcgatc 180
atggggcaaa caactctctc ataaccatca agctacaaat atgatagctt tactcatagg 240
ggccttgggt actggagtag ataaaggatc taaagcaaac atatggaaac aagttgttgt 300
tgatgtgatg gaaaagacta tgtttctctt gaagcatatt gtagatggct cattggatga 360
aggtgtggcc tatggaagct atacctcaaa atcagttaca cagtatgttt ttttggcaca 420
acgccatttt aacatcaaca actttgataa taactggcta aaaatgcatt ttgtgtttta 480
ttatgtctaca cttttgccag gctatcaaa aactgtaggc atagcagatt ccaattataa 540
ttggttttat ggtccagaga gccagctagt ttcttggat aagttcattt tacagaatgg 600
agctggaaat tggttagctc agcaaattag aaagcatcga cctaaggatg gaccaatggt 660

```

WO 2005/005597

PCT/US2003/027106

tccctccact gctcagcggg ggagtactct tcatactgaa tacatctggg atgatccaac	720
actcacccca cagcctcctg ttgattttgg cactgcaaaa atgcacacat ttcctaactg	780
gggtgctctg acttatgggg gtgggctgcc aaacaccag accaatacct ttgtgtcttt	840
taaatctggg aaactgggag gacgagctgt gtatgacata gttcactttc agccatattc	900
ctggattgat ggatggagaa gctttaacc aggacatgaa catccagatc aaaattcatt	960
tactttcgt cctaattggc aggtattcgt ttctgaggct ctttatggac caaaattgag	1020
gccaccttaa caacgtattg gtgtttgcc catcaccatc aagtcaatgt aatcagccct	1080
gggaaggtea actgggagaa tgtgcacagt ggctcaagt gactggggaa gaggttggtg	1140
atgcagctgg ggaagtatt actgctgctc aacatggtga taggatgttt gtgagtgggg	1200
aagcagtgtc tgcattattc tctgccatga gactgaaaag tgtctatcgt gctttacttc	1260
ttttaaattc acaactctg cttgttgtog atcatattga aaggcaagaa acttcccca	1320
taaattctgt cagtgccttc ttccataatt tggatattga ttttaatac atcccataca	1380
agtttatgaa tagatataat ggtgccatga tggatgtgtg ggatgcacac tataaaatgt	1440
tttggtttga tcaccatggc aacagtcctg tggctaatac acaggaagca gaacaggctg	1500
ctgaatttaa gaaacggtag acacagtttg ttaatgttac atttcatatg gaatccaca	1560
tcacaagaat tgcttatgta ttttatgggc catatgtcaa tgtttccagc tgcagattta	1620
ttgatagtto cagttgtgga ctccagattt ctttacatgt caacagtagt gaacatagt	1680
tgctctgtgt aactgactat caaaacctta aaagcagatt cagttacctg ggatttggtg	1740
gttttgcagg tgtggctaata caaggacaga taaccagatt tggtttgggt actcaagaaa	1800
tagtaaaccc tgtaagacat gataaagtta atttccctt tgggtttaaa tttaatatag	1860
cagttggatt catttttgtt attagtgttg ttattttaac ttttcaatgg cggttttacc	1920
tttcctttag aaagctaagt cgtgtgtgat taatacttgt tattgccttg tggtttattg	1980
agctcttgga tgtatggagt acatgcactc agcccatctg tgcaaatgg acaaggagct	2040
gaagctaagg caaatgagaa ggtcatgatt tctgaagggc atcatgtgga tcttctaata	2100
gttattatta cctcactccc tgggtcagga gctgaaattc tcaaacagct tttttcaac	2160
agcagtgatt ttctctacat cagaattcct acagcctaca tggatatccc tgaactgaa	2220
tttgaaattg actcatttgt agatgcttgt gagtggaag tatcagatat ccgcagtg	2280

WO 2005/005597

PCT/US2003/027106

```

cactttcatc ttcttcgagg gtggtgcag tctttggtcc aggtacaaa acttcacttg 2340
caaaacatcc atctacatga aaccagtagg agtaaacctg cccaatatct tacaactaat 2400
aaggacaaaa agcgaaaatt aaaaagaagg gagtccttgc aagttcaaag aagtagaata 2460
aaaggaccat ttgatagaga tgcgtaatat attagggctt taagaagaca ccttgcttat 2520
tacccaagtg cagctcctgt gctcagctta agtagtggtg gctggacatt gaagcttcat 2580
tttttccagg aagttttagg aacttcaatg cgggcattgt acatagtaag agaccctcga 2640
gottggatct attcagtgct atatggtagt aaaccaagtc tttattcttt gaagaatgta 2700
ccagagcact tagcaaaatt gtttaaaata gaggaaggtg aaagcaaatg taattogaat 2760
tctggctatg cttttgagta tgaatcactg aagaaagaat tagaataatc ccaatcaaat 2820
gctatctcct tattatctca tttgtgggtg gcaaacactg cagcagcctt gagaataaat 2880
acagatttgc tgectaccaa ttaccatctg gtcaagtttg aagatattgt tcattttctc 2940
cagaagacta ctgaaaggat ttttgccttc cttggcatcc ctttgtctcc tgcagtgtta 3000
aaccaaatgc tatttggcac ttccacaaac cttttttatc ttccatatga gggggaaata 3060
tcaccatcta atactaatat ttggaaaaca aacttgccct gagatgaaat taaactaat 3120
gaaaacattt gctggacact gatggatcat ctaggatata caaagtttat ggactaaatg 3180
ctgcaggctg gcaaaatttg cactaatgtg tcccaacctc ctttgtggat atgaactaga 3240
aaactttgtt tattcttgta catgtatgta tgtgtgtaga gtgagtgcgt gtgtccagta 3300
tgttatttgc acagagatat tttcaaaata ggcaccatat ttggcctagc aggatttatt 3360
tttatgttac cacttttctt gcctttgttt ctgaattttt tctgtctaaa atgtttctgc 3420
tacagaggtg tatattctgg ggctctgaaa tatgggggtt taatggactt taactcaact 3480
tctttggaaa ctattttatc atcttaggac ctcaaacact acaaacggcc ttgcaattgc 3540
tgctgtatct agtcatctct cgcctcttaa tatggactac aaaactttat gttttgaaaa 3600
cgtctaacat ttaccttgca cacaaaaacg agaaataaaa aaacaaaaat c 3651

```

&lt;210&gt; 21

&lt;211&gt; 2205

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 21

```

acatcctcct aaataatctt accaaggaat aatcaggaac agtcacgctt ctgtgtccct 60

```



WO 2005/005597

PCT/US2003/027106

tctctgttttg ctaaagctaa gcttatgtac caagttagaa catcaatgac attaaatgtg	120
gagacctttg ctactttttg ttagaggcca tccctatatt tgcttgettt tatttttaaac	180
cgtggaaatc tgaatccaga tagaacaaa attagggttt ttccatacc acatgctagc	240
atttgccactg attttcatag gaaaaaaaac ttcaaacaga acaaaataaa aacatgtagc	300
ctatagccat tcctatttaa aatgattggc ttccctggct aggtaaaatt ctgcatgatt	360
aaattgcca taattctgac atttgggttt ttgcatagat ttccaaaat ttaggtccta	420
agttgttatg gtaacttttt ttttaagaaa gttaaatttt aaattacaga tggattttgc	480
tgggcattag caatttgtgt ttatttagaa aatagagtgc tcttattttt gtaaatgtct	540
cacggaaata actaaatttg tttataaatt gagactacta aagcacatc gttgaagcca	600
tagagaacat cttgaaatgc agttttaagt ggagaatttt aggaaactta cataatatca	660
taactcaaat atattttaat tgcaattctc tcagccttta tactcatgtg ctgtatacac	720
agttactcta aacaatgtaa gagacatata cagtagcccc tagagttatg aatttttaag	780
tcaattaatt tccatgaaga aaattgagaa tggtgtttta tgtctgtata tgggtgtgatc	840
ctctagtttg tgcatgcatg tgtgcatgca tgtgtgtatg tgtgcatgta cacgtgcgtg	900
tgtatgtttg tgtgtgtgtg tgtgttgagt tttctcccaa tccttgtaat ataggaaatg	960
aacacttato caaatgttga gagttcattc acaccgcatc tgagttacta ggtcctggga	1020
cagtggaatg aggtattttt ctcttttttg gccaatttat ttaaatataa aacaatggtg	1080
ttagtcttag taggagttta gagtgcacaa gacttaaaat ttcccttgag agtggatttg	1140
ctcatgccta gcatctttgt gtatgtgcag aaaaggagag tagtgttagg ggctgctgag	1200
actatgggga gaaatgatga tacattgaag agctaggtct agggagagaa atcaaaaatac	1260
tcttgaaa ga taggaaaaca ttgacatagg gctacctcat atttttttta tttattttgca	1320
tgaataaaaa ctagaattat aaaattcaca ttctcaattg ggaattata tttgttaatc	1380
cataaaacta tttacattgt atgtggcaag ttgtagtcat ttttaagagt tagactctta	1440
ttgcttccaa ccaagaaaaa taaatgaatt cagtctagaa ttggcaagag taatgaagta	1500
ataattgtaa aaattgttgg agtatgtctt cctgagaatc atagtctcct gtatagcttg	1560
actggccttg aagaacagtg gtgacaacag agcctgatgt ctgttgaccc tttgagtctg	1620
tcattatttt atagacaaga tctgaagctc tgataaccct ggctaaaaac atttttaaga	1680

WO 2005/005597

PCT/US2003/027106

```

aaagaaagt actttaatat tatatatat tgttttact atcaatagt attgcttat 1740
gttatattta ttoaatggaa aacctgtat ttgtattgga tacaacatg gatttgatat 1800
ccttttcttt aaatatatta aatgaaatta aaaacatat ggggctttcc ttggggttga 1860
tttttcttcc cctataaaat gagtttctgt ggttcagaga caacctgaca gatcaactaa 1920
aatatgaaac tgtgagctg tgatctgaca gatcaactaa aatatgaaac tgtgagctg 1980
tgatgcttag ggcttcttgc acctaaagta ggaattatta gaaccagttc tttgttcaat 2040
gcattgctat gtttgactaa tgcgaatgg ttgctgtgca tcagaaaagg aagatattat 2100
tgagcttctc tcagtttgaa gaaggcaagt gaagtaacca gcaggtatta gcagagttat 2160
ttaaagctgc agactttaca ttaggggaaca cactcagata aaact 2205

```

&lt;210&gt; 22

&lt;211&gt; 4059

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 22

```

aaatatatat ggaagtatt ttcttaaacc cttaaagac caatcaaatg tgggtgtact 60
aattcttatg taacagatta actccaactg ctagaaggta acatgaaaaa tgccagcctt 120
gattggcatg tctgttgtat ttcttgacag cttgaaatga tgtgtgttga gaaatgaatc 180
tttccaggat ggtgctttca tttagtgcag tctactctag ctggttgctc tgaattttag 240
tccagacca aagctggtag gcaaccttat actttgccac tatggcaacc ccgcattgct 300
ggtgttaact gctgggtaag cactaaagag agagccgtca ggcgctctg cccattccat 360
ccctaactgt gcttcttcc cctgcctcct gtgctttctc tgatcaacca tcgacacccc 420
cttcctctg ctctgcgggt gaccacagaa gtctggaag caagtgatga ccatgagcat 480
atagtgaac agcctcacag gcaggttatg tttcgttctt ctgaactcag tccactaaca 540
cacaccatgg cttaggata ggaagaacat gtctaacaac tccctggacc aggggtgttt 600
gtactctgag tagcagtata actaatgaa tgactaaaat gccagcttg atttaactgc 660
ctgtccagtg cttcttgctc agctggggct ctctcctctc actccatagg gagaagaaaa 720
accaataagc tctcaccttt tccacttggg agtctaaagc ttagcttgat ccccatatgt 780
aatttcttcc ttctgtgtctc aagaagctct taatctatct ctatcattct ttaaatcctg 840

```

WO 2005/005597

PCT/US2003/027106

actagtctga gttatctctg tctttacaaa gtttactac ttgttgccta aaggataaaa	900
atctctgtctc atcagcatag cagcaataat tctcatgcc tggccttttg atttctttgt	960
cccatgatga tcttcagcca gttccagatg gtcactctct ctctgtagaa ggaaccacaca	1020
tgttcaagggt cctactcaga aaaggctctt cagttgccaa gatgcactgg atctacacaca	1080
ttatagttat tctctgtgtct ttgttcctcc attaatgtgg tgcttataat agtgggtatt	1140
agtatggtca tcatcattga ctccctagct gtccaagtgc caagaagaga ttgtctgcac	1200
gagtttgtat ttctctgagtt gttccaaact ttttggaaata cattttttct taaacacaaa	1260
tagtctcctc ctccacaaa ggctctgagc tctactcata gtttgtctct taaccccaag	1320
ctctctgggtt tgggtcaagca gtcacatgtg ccatcctact agccatggaa tgaatgacct	1380
tgatatcaac tcaaaaaact atgaccagtg aaagccaaag acacttggtt aggagacct	1440
gatttaacct ttcaggggaaa ctgaatgtaa gaaagaaga ctatgaccca gctccgggtat	1500
ctagtgaacg gagagacaga aaagctgccc ttggttcttg tgggtccccc gaatgcaccc	1560
cagtagcctt ctgctggacc cttttgtatg taggtcaaag gattggcttg gttctttgca	1620
acagcaagga ttctaacgtc tgtagggtatt ttcccttgag gcttgagatc tattgggtgt	1680
agaagctcag tccacacctt gttcaaaatg gtgtaagact tctaaattcc cttagtgcaa	1740
ggcagaactg tggccttaca agaataaagc ctatcttcgg tgccctaccta atatccctaa	1800
ctagggtctt tgaccttgcc cctttgtcct ataactccct cacttagaat gctttctctt	1860
ctctctctac ctaactacaa ctgttaoctc agaacctacc tcagggtgacg catcatcagg	1920
aagacccgtc ctcatacctt aagtcagccc atgtcacacc actgtctac ttgtctttgt	1980
tctctgtcac atggtaactc ctcaagggcc aaaaatggtc tcatttttagc tttagcattc	2040
tagagccaaa cagtccttgc ccattacag gcttgctaaa tggttataag tgaatggatg	2100
gggcatctca actcagtagt cattttcttc ttgatggcga cactgttcag agtgacatct	2160
gtccagcat catgtagcca ttttacctt agtttactaa agagaaagt tttaaaggaa	2220
taatatcttt agaggagaaa attaatgctt tattttttca ttaagttaa tacatatata	2280
gtaaaactga acatatgtaa agtagaatc tctttaagtg tacggttgg tataaatgga	2340
tgtaacctg tcacctctt taataattga ggtagccgaa tgttccctc acctaaagaca	2400
gtagatccct atatgcctt cctattcagt ctctgcaca ctcacagatg gggactccaa	2460

**PCT/US2003/027106**

41/186

WO 2005/005597

PCT/US2003/027106

<210> 23  
 <211> 1496  
 <212> DNA  
 <213> Mus musculus

<400> 23  
 gatttctgagc aaacacggac tgcacacacg gaggtcctag ccacctctctg atattgactg 60  
 tgaccactgg atacagaaat ggctaacaat ttactactacc cactggcaac gtctcatggc 120  
 aataactgtg atctctatgc ccaccacagc acagccaggg tattaatgcc tctgcattac 180  
 agcctggctc tcatcattgg gctggtggga aacctgctgg ccttgggtgt cattgttcaa 240  
 aacagaaaaa aaatcaactc aacctactctc tattcaatga acttgggtcat tcttgacatc 300  
 ctgtttacca cagctttacc cactcggaata gctactatg cgtggggctt tgattggagg 360  
 ataggtgatg cctgtgtccg ggtaactgct ctggtgttct acatcaacac gtaacagcgg 420  
 gtgaacttca tgacttgctt gagcatagac cgcttcttct ctgtggtgca cctctgcgct 480  
 acaacaagat taaaagaatc gaatacgcga aggggtgtctg cctgtccgtc tggattctgg 540  
 tctttgtcca aacactgccg ctgctcctca cccctatgtc taaggaggag ggagacaaga 600  
 ccacttgcat ggagtatcca aactttgaag ggacagcgtc cctgccgtgg attctgctcg 660  
 gagcctgtct gctgggttac gtgctgccta tcacagtcac tctcctgtgt tactctcaga 720  
 tctgctgcga actcttcagg actgccaagc agaaccact caccgagaaa tctggtgtga 780  
 acaaaaaggc tctcaacaca attatctcca tcattgtcgt gttcatcctg tgcctcacgc 840  
 cctaccacgt ggccatcatt cagcacatga taaagatgct ctgctccctc ggagccctgg 900  
 agtgtggggc gagacattcc ttccagatct ctctgcactt cacgggtgtc ctgatgaact 960  
 tcaactgctg catggaccgc ttcatatact tctttgcctg caaagggtat aagagaaagg 1020  
 tcatgaagat gctcaaacgt caagtgtgtg tgtcgatctc cagcgcagtg aggtcagccc 1080  
 ctgaagagaa ttgcggggaa atgacagagt ctcatgatg gatccactcc aaggccctcca 1140  
 atggaaggta aaggcacttg ggacttcaca gcacagcaag ctgogggatg ggccccggcc 1200  
 accgactggt cggctcccaa caaagatgcc ttccactgcc gccccacggc ccaatgcact 1260  
 gagatccaga ccagatcgag gagacaaaaa agcaagttca acttcataaa tgaatatata 1320  
 tgtatataaa ggaaggctct cataagtctc aatgtaaaaa gaaattcttt gtgaaattac 1380  
 tatttcttgt caatagtttg gcaaaagacg actaattgca ctgtatatgt ccagtgtaaa 1440

WO 2005/005597

PCT/US2003/027106

aatgttaata ctgtaataata tgaatatatt tottaattta cacctctttc aatttc 1496

<210> 24

<211> 1341

<212> DNA

<213> Mus musculus

<400> 24

ggtggcagct tttctacaat gaaggctgga aagaccttgt gagaaatgag agacaagtga	60
gattcctctg ctgcatgttt gccacatgt ggttctagc tcggtggcgg aggggcactg	120
ggtgctcatg tcaaaacggg ccagcttget gccattaaggt ttatggatgt cacaggggat	180
gaagagggaag aaatcaaaca agaaattaac atgttgaaga aatattctca tcacagggaac	240
attgctacat actacgtgtc ttttatcaaa aagaacctc ctggcatgga tgaccaactc	300
tggttggtta tggagtctct tgggtctggc tctgtcactg acctgatcaa gaacaagaaa	360
ggcaacacat tgaagaggga gtggattgca tacatctgca gggagatctt acggggcctg	420
agtcacctgc accagcacia agtgattcat cgagatatca aagggcagaa cgtcttgttg	480
actgaaaatg cagagggtta gctagtggat ttggagtga gtgccagct tgaccgaact	540
gtgggcagga ggaacacgtt catogggact cctactgga tggcaccaga agtcattgcc	600
tgtgatgaga accogtagtc cacatatgat ttcaagagtg acttgtgtc tttgggaatc	660
acogccatag agatggcaga aggtgcccc cccctctgtg acatgcatcc catgagagcc	720
ctcttctcta tcccaaggaa cctgcaact cggctcaagt ctaagaagtg gtcaaaaaaa	780
ttccagtcac ttatogagag ctgcttggtta aagaatcaca gccagcgcc agccaaggag	840
cagttgatga agcaccactc catacgagac caacctaatg agaggcaggt ccgcatccag	900
ctgaaggacc acattgatcg aacaaagaag aacgaggag aaaaagatga gactgagtat	960
gaatacagcg gaagtgagga agaagaggaa gagaatgact ctggggaacc cagctccatt	1020
ttgaacctac caggggagtc aacctgcca agggacttcc tgagactgca gctggccaac	1080
aaggagcgtc cagaggccct gggcgccaa cagctggagc agcagcagcg ggagaatgaa	1140
gaacacaagc ggcagctact ggctgagcgc cagaagcgca tcgaagagca gaaggagcaa	1200
aggcggaggc tggaggagca acaaaaggca gaaaagagc ttccggaaca gcaggagcgg	1260
gaacagcgcc ggcactacga agaacagatg cgtcgggagg aggagaggag cgctgccgaa	1320

WO 2005/005597

PCT/US2003/027106

catgagcagg aatataagcg c

1341

<210> 25

<211> 2368

<212> DNA

<213> Mus musculus

<400> 25

tcttactatt aagtatgggg atgattctgg tttttacaaa tgtgttagtc agattaaaga	60
aattgccttc tgttctcagg atttagagtg tttttattgt gaagcagttt tgaattttac	120
cagaggcttt tttaaaaact gattttgtgt atgcattcat gcccatgtct gtctgtctgt	180
ctgtctgtct gtctgtctct cctctccct ctctctctct ctctctctct ctctctctct	240
ctcacttgta tatgtgtgtg catgtgtttt cttttttatt gatatggctt attgcattga	300
ttgatttttc agttatttta tttatttgtt attttatgtg aatgaatatt ttgcatgcat	360
gtatgtctgt gccaccctg tgttactggt cctgaggag gccaaaagaa gtatgcagg	420
ccctcacact agaattgcag aaggctgtga accgccatcc tgagcttagg gtttaaatga	480
ggtcttctgg aaaagcagct gaaccacctc tccagccctt gatttttagg tttgttttta	540
attattattt atttttattg gctattttat ttattttaat ttcaaatgtt atcccccttc	600
caagtttccc ctctaaaaac ctccctccac aocgcccta cctcttttag ggtgtcccca	660
cacctaccca cccactccta cctcagtgcc ccagcatttc cccacctag attcagctct	720
taaactagct ttgcattcct ctaataaatt ccatttcaac atgccttaat tatcttcattg	780
tgttgatgaa tttgttttgt taattttttg gtggtaattt ttctatgttg catataggtt	840
aaattgttct atcgtttctt tttcttaatg actttttttt tggtttgact ctgatagcac	900
agtgatatta gcttcataaa atgtgttgat gtatccocat ttctaataatt tggagcagct	960
tctgagcatt tttcaatttt tctttaaaca tttttgaaat ataogcatca aagatatttg	1020
gtccaggatt ttctttgttg atagttttat tattattatt attattatta ttattattat	1080
agattcagcg tctttcctaa tgcattatta cctatttttt cctgatttag ttccagtgga	1140
aactagctta tttcaatatt tttatagtat ttattaagcc ttctcatctt tcatctgggt	1200
ctttctataa tgtgtcattt tctccatctt cattttaaac tttctatagc ttcaaacctc	1260
aaatgcttct tattgggtatt atgactgatt atttttatgg acttatctaa cttgtgtaac	1320
tatgtgtaga gtgacataag gatccagtta ctgtatttat ttcccgtaac ttttgttgt	1380

/

WO 2005/005597

PCT/US2003/027106

```

atgtagtggt ttgtctgaac gtgtgggtctt tgtaccacct tgtgcagtggt ttacagtcac 1440
ctatgtatgg ttaagggttct cggggactag agttacagat agttgtgagc cactgcacgg 1500
ctgctagaaa ccaactctgc tcctctggag gagcagccac tgattcaggc cctaaccagt 1560
atttctgttt tgttgtttta ttgccactta aaagttttgcc ccacttgtga tcttacattt 1620
ttcaatttaa aaaattacag cacagatagc ttcaattta taatcagttt gaaagtgttt 1680
caaatattat ttcataaaaa attttatgat actgggtatc acaatcttac ccaaatataa 1740
caaaatatgt ctttaggaaa agaagaaatt acaggccaat ttatcctaaa aaaaaaaaaa 1800
aaacaagaac agaacacttt ttaataaaat actgacaaaa ccaaaatcat cactatatgt 1860
aattaattaa tggcatgcag aagttttttt caaaggaatg gaagggtaga cctgaaagct 1920
ggtaaaaaga atgcattgca ttctaaattt tactcatcga tattgaataa aattcttaca 1980
ttttgttatg ttctatgaa gaaaaatctc ttaaaaatag aacgataaca ctaaagctat 2040
ttaaatgcaa tgttaggggt ttgttaatgt agagaaaaca attttcattt tcaaatgttt 2100
gggttatatg ataattgtga gagttcttta gtgatgacat gatttttttt ttctctgagc 2160
tacaaaaagt cccaaagtag aaattaaagt taaatttttc taaatcctta attaatataa 2220
aaaaaagtgt catgctgagt gtggtggcca aaggcagggt aatctctgtg cgtgtagggc 2280
agcctggtat tcattgcaag taccaggcca tccagtgcta catagtgagc cctgtcaac 2340
caatgaagca gagacaaaga aacaaacc 2368

```

&lt;210&gt; 26

&lt;211&gt; 1941

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 26

```

aagctagcct tgaactcaga agtctgcctg cctctgcett tcaagtgcgt gaaataaagg 60
tgbtggccac cactgcctga ccataaaatt actttttatg tagaattttt tttttttttt 120
tttttttttc tgagacaggg ttctctgtga tagccctggc tgcctggaa ctcactctgt 180
agaccaggat ggcctaaaa tcaaaaatcc gcttgccctc gccctccagg tgctgggatt 240
aaaaggggtc gccaccacca cctgactaga atttttatat atactttgta tatagaaata 300
ctttttatat agatgggtcat gttctgtata ggctatctag cagtcttggt tcacaacctt 360

```



WO 2005/005597

PCT/US2003/027106

tccatgaattt ttagggtctt ctgtgtgtga tctaatagagc ttctgtgctt atttcagagt	420
aacaatcttt gagggtagca acttgtaaat acagaatgtt tagcctagat tactgtaaaa	480
attaaatgtt ggatgaattt tgaatagggtt tgaacgaact atttacttat gaaggaaaca	540
ttagttaatc ttaccactc ctgttttagct ttcactaata aagaaactcc tcaagtcttc	600
aggtaatttt catgctcact gagtgtctcag tacctgattt cactggtggt ctaagacttt	660
taccctgagg agttatcata tcttcagtta atcaggaaac tgtgtcttaa gtatttgtta	720
tggtgatcat ctatttttca atttaccoga tcattatcaa taaactgtta atgtacttga	780
tgataagggtg tgattacttt atttctata gtgtattctg tatctctgta ctcccagag	840
tcagatcttc ccaattcatc ggttgtttat taagccctta actgttttta tagtgttagg	900
ctatttgaat ttatgatgtt taggtagttt gccataaagt atgggcataa tatccctgtt	960
cttttgatcc tctattgtt gatgtactct gtaagccctt gtctattgtc tatgtttgta	1020
aataaggctg tattttaaat gtgtagtttt ttttctctc tccagaagga tctgcttttt	1080
catttagctg aaagtgttta aaaatcatgt ctgtctgtaa agatgacaac agctcccaagt	1140
aacacagaag cctgtattgt gtgagctata acttggaaga atttcagata tacaatgtcg	1200
tagtgatttt ctataacaat tttttattta aaaggagaa gaaactggct ttgtactctg	1260
tgaatttcoag ctttgtgttg tctatacatt gctcctagt ccttggtaat gctgactatg	1320
atgacatttt tgttacagtc ggcgaggctc tggcctgggc aagagaggag cagctgaggc	1380
cgcggcgcaa gagaaaatgg cagaccctga aagcaaccag gagacagtaa attcctcagc	1440
tgcccggaac gatgaagctc cccaaggagc tgcagggtata ctgactggca cttaaaacac	1500
acatatattt ttgttctgtt cacaatttta tctttggatg aattttcttg ttctacatcc	1560
taagtaggat gaaaggaggg gagagaatta agaggttacc atgaaacact tttatttttag	1620
gtcatagatt ggggtctctt gatttgtggg ctcatgtgtt gtttaagactt aaactctcaa	1680
gcagtcata catgtactac ttccagaggg atttatagta aggtataaat ttccattta	1740
aggtttttat atattgctta gagttgacta atgattgttt cattgaattt aaattcataa	1800
taaaaaagta aagatgtatt tgaattgctt tctaagcatg tagatcttag cattttatac	1860
gcctaaaaa tttgttttgt tctgaagcta ctttagtaat atttagattt ttatgggctt	1920
atttgatctc ttggattgcc g	1941

WO 2005/005597

PCT/US2003/027106

```

<210> 27
<211> 1940
<212> DNA
<213> Mus musculus

<400> 27
aagctagcct tgaactcaga agtctgcctg cctctgcctt tcaagtgcctg gaaataaagg      60

tgtgtgccac cactgcctga ccataaaatt actttttatg tagaattttt tttttttttt      120

tttttttttc tgagacaggg tttctctgta tagccctggc tgtcctggaa ctcaactctgt      180

agaccaggat ggcctaaaaa tcaaaaatcc gcttgcctct gcctcccagg tgtctgggatt      240

aaaagggtgc gccaccacca cctgactaga atttttatat atactttgta tatagaaata      300

ctttttatat agatggtcac gttctgtata ggctatctag cagtcttggt tcaaacacct      360

tcctgaattt ttagggcttt cttgttgtag tctaatgagc ttctgtgctt atttcagagt      420

aacaatcttt gagggtagca acttgtaaat acagaatggt tagcctagat tactgtaaaa      480

attaaatggt ggatgaattt tgaataggtt tgaacgaact atttacttat gaaggaaaca      540

ttagttaatc tttaccactc ctgtttagct ttcactaata aagaaactcc tcaagtcctc      600

aggtaatttt catgctcact gagtgtcagc tacctgattt cactgggtggt ctaagacttt      660

tacctgaggg agttatcata tcctcagtta atcaggaaac tgtgtcttaa gtatttgtaa      720

tgttgatcat ctatttttca atttaccoga tcattatcaa taaactgtta atgtacttga      780

tgataagggtg tgattacttt atttccata gtgtattctg tatctctgta ctcccagag      840

tcagatcttc ccaattcatc ggttgtttat taagccotta actgttttta tagtggttagg      900

ctatttgaat ttagatgatt taggtagttt gccataaagt atgggcctga tatccctggt      960

cttttgatcc tcctattggt gatgtactct gtaagccttt gtctattgtc tatgtttgta      1020

aataaggctg tattttaaat gtgtagtttt tttttctctc tccagaagga tctgcttttt      1080

catttagctg aaagtgttta aaaatcatgt ctgtctgtaa agatgacaac agctcccagt      1140

aacacagaag cctgtattgt gtgagctata acttggaaga atttcagata tacaatgtcg      1200

tagtgatttt ctataacaat tttttattta aaaggggagaa gaaactggct ttgtactctg      1260

tgaatttcag ctttggtgtg tctatacatt gctcctagtg ccttggtaat gctgactatg      1320

atgacatttt tgttacagtc ggcgaggctc tggcctgggc aagagaggag cagctgaggc      1380

ccggcgggcaa gagaaaatgg cagaccctga aagcaaccag gagacagtaa attcctcagc      1440
    
```

WO 2005/005597

PCT/US2003/027106

```

tgccccgaca gatgaagctc cccaaggagc tgcaggtata ctgactggca cttaaaacac 1500
acatatatatt tgtttcgttt cacaatttta tcttttgatg aattttcttg tctacatcc 1560
taagtaggat gaaaggaggg gagagaatta agaggttacc atgaaacact tttatttttag 1620
gtcatagatt ggggtgctctt gatttgggg ctcatttgtt gttaagactt aaactctcaa 1680
gcagtcocata catgtactac ttccagaggg atttatagta aggtataaat ttccatttta 1740
aggtttttat atattgccta gagttgacta atgattgttt cattgaattt aaattcataa 1800
taaaaaagta aagatgtatt tgaattgctt tctaagcatg tagatcttag cattttatac 1860
gccctaaaaa tttgttttgt tctgaagcta cttagtaata tttagatttt tatggggctta 1920
tttgatatct tggattgccg 1940

```

&lt;210&gt; 28

&lt;211&gt; 2935

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 28

```

tgtatctctt tcatcaattt ttctctgtgg tatagcaaat gaccacaact caggagcttg 60
gaatagtagt tttattgttt gtgtgttttt atggatcaac tgggtctctt tattttttgt 120
tggtgttttg ctttgtttct tggttttttg agacaggatt tctctgtgta gccctgaact 180
ccgtttgtag accaaaactt ctttgaactc agagaagtaa gcttgcttct tctctctgag 240
tgctgggato aaagacatgt gctgctacca ccagcttca gctgagtagg tctcttatto 300
aggcatcacc aggtggcctt acagtgttag ccaggctatg ttccctctct gagcttcaat 360
cttcttccaa gccctctctg tctgctggca gattcctcat ggtctgaaag aatgaagctc 420
cattttcttt ttcttttttt tttttaagat ttattttatt tattatatgt aagtacactg 480
tagctgtttt cagacactcc agaagacgga gtcagatctc gttacggatg gttgtgagcc 540
accatgtgct tgctgggatt tgaactccgg acctttggaa gagoggtcgg gtgctcttac 600
ccactgagcc atctcaccag cccaaagctc cattttctag ccggttgta acagaccatt 660
cctagctact gtgttatgcc ctcccttggg agtgcattgt agctgtttgt gtccctctat 720
gccagcaaga gcagcctctg ctttggaagt gtcacccat gtgagggcag aaggatcgag 780
gagttcaggg tcatcttcat ccacatagcc cgcttagaca acatgagacc ttgtgtcaaa 840

```

WO 2005/005597

PCT/US2003/027106

agaaatgaac aataggagct ggcaagcttg ctaagtaa at gaggatgttt gccaccaagc	900
ctggcagctt gagctcaatt cctaaaattc acatggt aag agagaaacaa tttccataac	960
ttatcctcgt tctgcccaat aaataacaaa tgcttttttg tttgtttctt tgttttgttg	1020
gttttttaaa atctttttta aagcgctcat gtggtaggat tgatcagcga gggtaagttc	1080
cactctgtgg gttggtagca ggactctgga gaagggcagc ctgcacctt tgttagtctt	1140
acttacaag aaccaaattc taagccccag tgaggacctg cttttctgtt tttttctctt	1200
ttcttttctt ttcttttctt ttcttttctt ttcttttctt ttcttttctt ttcttttctt	1260
cttttttctt tttttttttt ttttgagaca gggtttctct gtgtatccct ggctatccgt	1320
gaactcactc tgtagaccag gctggcctcg aggatctgct tttctgatcc ctgtgatata	1380
tgtttagtag ttcatagggg tttgttttgc aactgcagtg tttgctaaat gcattctcat	1440
attttctctc tgaccctggc tctgtttcat aatgccgaga tcgactagct cttttatagt	1500
cactaatcca gttaggaatc tctgtctgt ctccacaag ggaggaaag atgccaaga	1560
aggaggtctg atctaaagag agattatttg ttgtcactag gttgaaagag ttgtgcagct	1620
atgcaagggt tgttgtccta gggggcattc tttagggct agtcattatt ttgttgagtg	1680
tttctctctg gcctctagag ctgaaaactg aacctagggc tttgtacttg ctaagcaagt	1740
gttctatcat ggagctaaat ccccaacctt tgggtggtta gtcattagca ccattctctc	1800
tgaagcctgt gatagctcac acctaaattc ttggatggtc tttttctcag aggctcaggt	1860
atgaggagct agtgaatca cttagccaaa tatctctgtc tcgtagctc agggcagctc	1920
tggacagaga gccttcaggt aaggagtggg gactgtgtga gggagacttg gctcaggagg	1980
agctgggttc tggtcaggc tctgtttaag ggtagtcctc gaacatgcac ttgtttctgt	2040
attcactaac aatataatat ttccatttat ccaaggttct gaagactcag aagatggagt	2100
agaaatggca acggcagcaa tagagactca agggaagctt gaagctagca gtgtacccaa	2160
ttctgatgat gatgcagaga gctgccccat ttgcctcaat gcatttagag accagctgt	2220
gggcacccca gagacctgtg ccattatttt ctgcctggat tgcattatcg aatggctcag	2280
ggtgagttgg cttttcagtg ggctactgct acccctatg actaggtctc ctctctgcga	2340
gcaaaactga acacagggtc gagtgctgcc tgggttctca gcattgtggg gaaggaatgc	2400
ttactgtggg ggctgttact gggtgagaaa ggaatgactc ggcttttctg agggtcaggga	2460

WO 2005/005597

PCT/US2003/027106

cacaaactct teggcaacct cacatagtaa gtgtaaggca gcctctgtag gtattggaat 2520  
 ggtgcaagtg tgcttactca gttctgatgg caagtcatga agagacaagc ttttatcacg 2580  
 ctgcttacct tgcagtgaa ctttaaggaga ctgctctggg ccttcacca ctggcaaaga 2640  
 cttttatatg tgtacaggta tgtggtgtgt gcctgtcttt acacgtagag gctaaaggat 2700  
 gtcaggatct ctgctctgtc gctttctgcg ttattccttt gagtccagat cttttactga 2760  
 agctgcagca taataggcag ctagtaaacc caagacattc tctcattctt catggcatta 2820  
 gcattgagag atgaaggat aatcttgccc aggtttttat gtggatgttg agatatgagt 2880  
 ttgggtcctt gtgtttgcat aacaaatttt cttatctgtt gagccatccc catcc 2935

&lt;210&gt; 29

&lt;211&gt; 4090

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 29

taccctaaata caagtaccag ggtggggagc tacaaggcct cctgtgtga tctgggacat 60  
 gaaggggcaa gggcaagggg attcctgaag ggaaggggtg gcattcaaat tctgaaagcg 120  
 tggagatctt tattagcaga cagaggtctg ggcggggcga ggcagctggc aggggttctg 180  
 ccatcattgc tggctccagg aggcagacaa cagaagctct ggaggcagga aatccaggtg 240  
 gcgggtgtct actttcatct gcctccggcc ctccaggcca gcactggctg ttgtccagca 300  
 tagcgggtga cacagcttgg ggggacacgc agaagaagc cagcagccgt tctctccaac 360  
 tctccagggt ttccattggg atgcggctgc gcttgagcac ggaccgcagg gcagggctga 420  
 tgcgcctgaa gcactctgtg ggtgtgaaga cagggtcctc tctcctctgg tctccccac 480  
 ggccaggccc acgtctccgc ttgcctggc tctcatctc caagtaacgg agcactcgct 540  
 cttgtctctc tcccagcggg ttcataaaat cattccagac ctccacatag gtggcattgc 600  
 tgcaggcctc tgcgaagatg ccagggtcag caggagtcag gagggccccc ttccagtaag 660  
 actggagaga gtgtgtcagt gccgtctgct atggagagtg aggaagccgc agaagtaca 720  
 gatgacccaa tggagcaaga ctaactactc agaaacactt agaggcagta ttttacatac 780  
 agttctgggt ttacactgta taagactttt aagtaataaa gtggaccttt agttttacaa 840  
 gagaacacgg ctgtaaaaa aagaacctta agaataaacc ctgaagggtg tatgtggaag 900  
 agctgtgagt acggctcctc tgggtccccg ttagtgtgta ttttcttgtt tgggttggtt 960

WO 2005/005597

PCT/US2003/027106

```

ttttgtttgc ttttttctgc gtgtactcaa atcagtgggt tgtgtataga tttttttttt 1020
aattdtagaat taaagttttt aaactggaag ataattataa ttttgaaaac tttaaagatg 1080
atctcatttg gtttatacat acacaaggaa gattttttgtc ttgtctctag cagtttccat 1140
attttggtea tagtttaaac atgttaacat gtgaattaat agggtttcat gtggtttcag 1200
atttttattg ttogactgta caatggaacc ttaagtcata tatacatata tagattatcc 1260
tgagggggga tgttatattt ttctgtttct ataagagatg aatacagtgg atactttttt 1320
attggtaatg actgagttca cttctttcag aagacatctt ctctctctag tagttgagac 1380
aaaaatctgg cccctgtgag accctgggaa tctttcagtc tgttgaaata ccagggttaa 1440
cacattccaa gagatctgtg caaactaaat tcttttgat acttctaagg tgcctgagac 1500
aacaagaact cattttatta tggaaagtgt gctttatctt gggagtgtgt ctcaagcatt 1560
agcttctgtc ctgtagaatg agtgcttcgg agcctgacat gaaaccatct caagagccca 1620
caggctccat aacattcggg tgctttttctg aacactgtca acatcacatc tgtctttctg 1680
aataatccta tatgcgcgat ggcactgggt tgaacaatca ctgtactgga agaattagta 1740
gaggacttca gtaatgtacc tgagctaaaa tgaccgaggc gttaggggtg cacagaaaac 1800
accatgattt gtataacatt ttgaagtga ttaatatattt tgaacatgct tcttcaacag 1860
ccagtgttat atttttcaga tcaacacaaa gcacaatggt tactactcta taaactcaat 1920
attttcaaat tcacatatat aaagtcatgc aagctgcaac ttccctgtca gaattactgg 1980
ctgccaaatt tatacctgtt tcttcagctg tactttttga tatttagaat ttttaaaatt 2040
ctgtaaagta ggttttttag actgtaatgt gttcaactgc tttgtgaagc ggtatatatt 2100
ataatttcgt gtgtaactga atgcttgggc tttcaatata gtattcatat aaagcaataa 2160
atattaatgt tatgaaatat tggagtacat ttttatcaaa atacaaaatc tcttttttag 2220
tttcagacat ctgaggtaga gggatggacc taatagctga tacaacagc ttctcacact 2280
ttatctatcc taagcttcgg gtgatcagag ggaaccaca aggtttgcat ttgactgct 2340
tagacgttac tatggctaaa aagatatattg gctccgtttg ttcataaaag aatattgtac 2400
tgactgatga ccttcagggt cacagcagct ggacagtaga tttatgaatc tgtctagtaa 2460
aactgtcgat ttactgtacc caaaggggtg aaagtcaaat gtaacttcaa gttttttggc 2520
aaaaagatta aaatgaagca aaatttaagt gtgacattca tttgtaaatgg cctgttagag 2580

```

WO 2005/005597

PCT/US2003/027106

ttgagggatt gacagtaaga gcagatttta aacatttttag gtttagagtt tttgagattt	2640
tccttaggat atttatgagg ttgttgtcaa taaacctgtt ctctaagctc ctgtgacctt	2700
tgatagtctt tatttatggt gccatggacc atttacaac aagtcagttt gctgttggtt	2760
aaaagttgaa gatttcgcat catgaataga ggtctgtggc tttatttgta aacttgcaat	2820
tgctatcttt gcaaggggaa gtgtatttct ttattaaata aagtacaatt aataatgggtg	2880
aatgtaccaa aatgacatca ctcaattcta tgagaggtct gcattttaac ctatagttta	2940
atagctttaa tatttatttag ctattcctat gttgatcata gatgaaagt gttgtgcttt	3000
atacagatac acgtaggata ctggtgaaag gtctctaggg cagttgtaat attcatcacc	3060
gtgtgaggcc atgttcagac tgtggatgca ttggtccctt ggaagtcctt ttccacacgt	3120
gggtgttagt gcacttacag gagactgcag gaaagtgta gttctaata gcaactgagtc	3180
ctttgtgagt gacagaatga gacccaagag ggagggtcaa gccgtcccggt ggctgaagta	3240
gctggctctt tgatgttgaa cagattccta accgggttct cctttcccaa gcttaactca	3300
gatctgggca gtgctgatgg tgctgacaga atacacatga catgggttttg ccacccctcc	3360
cttttaaaaa gtgaaaacat tttgaaaact ctataaagtt ctgtacatgt agaacagaag	3420
tgagtagtga aaatatattt tgaggatttag taaacttaatt ccacttaatt gtcacaactc	3480
cggtctttcc catatgtagc cagagcaatg gagttacaac tctggctttc gaaagctatt	3540
ccagaaaccc tgccccagaa agtcttaag cattgagatc cttgtgtttt attttggcag	3600
tgtagatagg catgtattta tgcatttgta aaatcaattt ttttcaaata atgtatgtaa	3660
tgtactagct taaacggtac tgggcagagc cttagagctac tgcgaggatt gaatgtgaag	3720
ccggtatcgc gggtggaat gtacctgcag agctacagca aactattcog ggtagtgttt	3780
caggctgcct ttgagcagga gtttcttaga tctattgggt ttgacaaact gaagatcagt	3840
tcttgagatt tgtgttaatc atgagatgaa tggatgcaaa aaaccccttg taatttcagt	3900
tggaattatg aaaattagct tgatgggata ttggcctaac aaggatgatg gtatgtactg	3960
gctagaatac atatatttca catataaaaa ataatccgga caccagaatt ctctctcttc	4020
aatttggagc ctagatcgat cactttgcc aataaatgta ttattttcat aatgcaataa	4080
agtgtaaact	4090

WO 2005/005597

PCT/US2003/027106

<210> 30  
<211> 3272  
<212> DNA  
<213> Mus musculus

<400> 30  
 tttttttttt ttttttttgt ttcaagacac agtggcccag gttggcctag aactcactat 60  
 gtagcctatg ctggcctcaa attcacaaca ctcttcttgc ttgtctctcg aatgtcggga 120  
 ttgcagggtc tgttcatcat gtctgggtta ttagtagctg gaaatagaag gcagggttcc 180  
 atgcacacta ggcagggtct ctgctagagt agtggatcaa tgcagtgac tgcattctgg 240  
 gagttagtga tcaatcgagc tgactgcacg tggggagtag tggatcaatc gcagtgaact 300  
 catctggaga gtatggatc aatcgagctg actgcactcg gggtagactg aagctgtctg 360  
 gggacatttc cagttaacac cactgagatg gatcaggctc cagcagggtg ggcaagggtc 420  
 gctgataagc atcttgatgt gcaagatgt tgcttacaat gagctagcat ctggcccaaa 480  
 tgtgggaaag tacaaaggct taaagtagac tgaagtctcc acgtgcaggg gatctgtgaa 540  
 gctttgtctc ctgctgccag ttggtgctaa ttacttgtgt gtcactgtaa ggggaacctt 600  
 gagggaattt gtgtgggaag aaagctgttc ttgggtctct catttcagag ggcctcaatc 660  
 cagtcctgca ttgaagttag cctgagtgcc ccctgctgtg acctcatact ccaggcacct 720  
 gggactgggg tggtcagatc agggataaga tggccagttc tgtctgattt tgactttcag 780  
 aaaagtgaat gaagagttat ctagtgcagg tgtgtcccac accagtgaag gacatctgtg 840  
 ctgttactcg gtaggatcta gcagtcgcat cccaaagcaa ttaagttact aaccagagta 900  
 ctgggcagtc acctgaacaa cattcttctc cttagaaatc ttccaagcga acccccaga 960  
 caactctggt tactgatagc tgtccataga ctgataggca gtctcccttg ctgaagacaa 1020  
 cacctacata actcactgaa cacggagagg tcatgctggt gcccttggcc ctgcagacta 1080  
 gtgtccgtgg ttctgggagg tactctgcat gctatcagag gagaagggtg aacaccaacc 1140  
 cagatacaaa tctttttatc tgcaatgggt accttctgct atgagatgct ggggcaatgg 1200  
 cggcactaag gttgtagaag taaccacac tctctggatt taaagaactg catgggatag 1260  
 agcccatgcc tcacgtgac ttgggtgccg ggaacctgag actacataaa ccatgacctc 1320  
 gggggaaact attgttctgc tcaagggtta tagcaatata acaattccca atgtcactct 1380  
 gctgtactca cagatcagca cctgtctcag ccatcatcag agaagcttcc ctctttagta 1440



WO 2005/005597

PCT/US2003/027106

gatgggaata aatacagaga ctcaacaact ggacattgtg cagatagtga aagacattgg	1500
aacactcagc cctaataatgtt aacaggaact atgcagatga ggaggtggag ccagagggga	1560
tggagggctc caaggaacaa gtgccttcca ggcccaacag aactgatgca catatgagct	1620
gacagactgt ggcagcgcac agggcctatg cagggtccaaa ccagatgggt ctcgactctg	1680
aggtggggga aggagacata agctctctat cctaaccctaa agctataact aacaactgcc	1740
tatgaaggaa aaaattaatt tctccaagag tatcttactg gatatacaaa tacaattaag	1800
ggcaggtccc atgctcagga aaacatggtg aacaccacaa gtaactctg tgtgtgtgtg	1860
tgtgtgtgtg tgtgtgtgtg tgtgtgtgag agagagagag agagagagag agagagagag	1920
agagaagtca tggatagccc tgggtttgtt tgtattttga tgctaattcc gattccctaa	1980
gaggggctgc ctaggaggag gagtgaatca cctactcagg tgacttcatg tgaccattct	2040
aatgaataaa gatttcaagg aaaccattcc ctggacgggt aggcgggtct tccaggtcag	2100
acgggcatgg cgggggtggg gtggggcaaa agaggagagag agagtgggct ggaggacagg	2160
agcataaaga cgaataatgta ggtagtgaat ccccgctccc ccacccctg ttccagtggtg	2220
cagatctgtt tgggtcagct accagaggat ttaacttaga atggctgata aattaggatg	2280
ttaattgttg tgcccagtga ttgagttacc gttgattctg aactaagttt gtgtgtgtgt	2340
ttctttcact tggcggctca actgggttcc ggagagaaaa ggtacagtga tgtggaatcc	2400
cagccagcca caggaatttg gaagtgtgga gctggcatgg cagcttaaca agcagggtgg	2460
agagctccag gacgagagag tctgctgaga agaacaaggc ccgccagtgc cttgctggca	2520
atagcatgga tagtttcttt ttacatttcc tgctgtgtgt atgtgtgtgt gtctatgtga	2580
gtgtctctgt ctgtgtctat gcatgtgtct gtatgtcttg tgctcttttt tagtttcttt	2640
tttgtttatg tgtctctggt ttgttttaac cttgaatgct tgtctttttt atatgcctat	2700
ttttttttaa gagagaaaga aggtgtgggg ttgaaagggt ggagaggtgg aaaggatctg	2760
ggaggagaca agggaaggga aaacatggc cagaatatat cacatgaag taactttatt	2820
ttcaattaaa aaaagaattt tcccattatg gttatgaggt agcaatgaac actacgggtg	2880
ggggtcagca catgaggaac ttgtttaaaa gactgcagca ttagaagggt tgagaaccac	2940
tgtcctatga actctctggc gtctctcatgt tctccaccc tgagaaatcg caatactgct	3000
gtatttactg tcgctgcgaa accctcccta aggggtgggt agatggctca gtgagtggtt	3060

WO 2005/005597

PCT/US2003/027106

tcttctatct tccacccttc ttcactcctt ccccaccctt tcaacctcca acactaaata	3120
ggaaagaaaa agaatagaga ggaaaagggg gccaccttat tgctagacta ctctctgctg	3180
attaaagggtg tccagttcct tgggtacctc tgatctttgt catcaggata tctattttcc	3240
tgttgttgtt tcttttttgc tcaagactac tc	3272

<210> 31  
 <211> 3821  
 <212> DNA  
 <213> Mus musculus

<400> 31 gcttttggaa accagagact ccgagggagg cgaccaggct gcggaggaga gggccggctc	60
acaaagtgtc gctttgacac atccttagga tggaaagtaa gtgaaaacag aaccacacaa	120
aacaaaactc cgcgaagtgg tgctgctacg gaggaaccaa aggggagaaa aaccgggtgg	180
gcaggctcaat ggttgcttcg cagcgtttg gcaagtttgt ggaacacttt cttaggaatta	240
ggtctttttt gtaccccatc catctctctg acttcogaag aaagaagttg tgtttggatt	300
gcaatggagt ctaaggagac agggctagac gcacgtgaat agtcccgcca gctgggctga	360
atttgtggga atttagaaag acagcctgtg gaagtgaac gtctctgaag tcccctggg	420
ttcattcgga tggcacctaa cgcgtccgtg gacagacctc ttcaccaaca gcttcgatg	480
ttgccatttt gctctcttg accttaatta atctctagga aagtctaaac ttccgacctc	540
cctctttttt tgatacttat tttttgtact tctgctctct gggattgggt tcttaacaa	600
cctggatcct ttttcatatg tcaaaatgaa tctctgatg tttaactat tattgtctt	660
tggattcttc tgcattcaga ttgatggatc togtotttgt caagaagact tccccccag	720
gatcgtagaa caccctctct atgtcatcgt ctccaaggga gagcccacca ctctgaactg	780
taaaagcagag ggcgcagcca ccccaccat tgaatggtac aaggatgggt agaggggtgga	840
gacagacaag gatgatccca ggtccacag aatgcttctg ccagcggat ctttattctt	900
tttgcgaatt gttcatgggc gcagaagtaa accggaagaa gggagttagc tttgtgtgc	960
aaggaaatat cttggtgaag cagtgagtcg aaatgcattc ctggaagtgg cattattgog	1020
agatgacttc cggcaaaacc ccacagatgt ggtagtcgca gctggagagc ctgcaatctt	1080
ggagtgccag ccaccacggg gacaccaga accaaccatc tactggaaaa aggacaaagt	1140
cgaattgat gacaaggaag agagaataag tatccgtggt ggggaagctga tgatctctaa	1200

WO 2005/005597

PCT/US2003/027106

tactaggaaa agcgatgctg gcatgtacac ctgtgtggga accaatatgg tgggagaaa	1260
ggacagcgac cctgcagagc tcactgtctt tgaacgaccc acatttctca ggaggccaat	1320
taaccagggtg gtgctgaggg aagaagctgt agaattccgt tgtcagggtcc aaggagatcc	1380
ccagccaacg gtgagggtgga aaaagatga tgcagacttg ccgagaggaa ggtatgatat	1440
caaagatgac tacacgctga gaattaaaa ggccatgagt actgatgaag gtacctatgt	1500
gtgtattgct gagaatcggg tgggaaaagt ggaagcctct gctaccctca ctgtccgagt	1560
tgcacctgtt gctcctccac agtttgtggt taggccaaga gatcagatcg ttgctcaagg	1620
ccgaacagtg acattccctt gtgaaactaa aggaaccca cagccagctg ttttttggca	1680
gaaagaaggc agccagaacc tacttttccc gaatcaacct cagcagccca acagccgatg	1740
ttcagtgctg cccacggggg acctcaccat caccaacatc cagcgttcag atgcgggtta	1800
ctacatctgc caggccctaa ccgtggcagg aagcatttta gctaaagcac agtggaagt	1860
tactgaogtt ttgacagata gacctccacc cataatcttg caaggaccaa taaaccaaac	1920
acttgcagta gaoggtacag cattgttgaa gtgtaaagcc actggtgagc ctctgcctgt	1980
aattagctgg ctaaaggagg gctttacttt tctggggaga gatccaagag ccacgatcca	2040
agaccaagga acactgcaga ttaagaattt acggatatct gatactggca cttatacttg	2100
tgtggctaca agttccagtg gagagacttc ctggagtgca gtgctggatg taacagaatc	2160
tggagcaaca atcagtaaaa attatgatat gaatgacctc cggggaccac catccaaacc	2220
tcaggctcact gatgtttcta agaacagtggt caccttatcc tggcagccag gtacacctgg	2280
cgttcttctt gcaagcoggt atatcattga ggctttcagc caatcgggtga gcaatagctg	2340
gcagacagtg gcaaaccatg ttaagacaac tctgtatata gtaagggggc tgaggccaac	2400
acaactctact tgtttatggt cagagcgatc aaccacaaag gtctcagtga tccaagtcct	2460
atgtoggatc ctgtacgcac acaagatatc agccccccag caaaggagtg ggaccacaga	2520
cagggtgcaga aggaattagg tgatgtogtt gttcgtctcc ataaccagtg tgtcctgaca	2580
cctacaactg ttcaagtac atggacggtg gaccgacaac cccagtttat tcagggtctac	2640
agagtgatgt accgtcacag ttccgggacta caagcctcaa ctgtgtggca gaatctagac	2700
gccaaagtcc cgactgagag gagtgtgtgc cttgtgaatt tgaaaaaggg ggtgacttat	2760
gaaattaaag tccggccgta ttttaacgag ttccaaggaa tggacagtga atcgaaaaa	2820

WO 2005/005597

PCT/US2003/027106

```
gtccgaacca ctgaggaagc cccaagtgcc cctccccagt ctgtcactgt gctgacagtt 2880
ggaagtcaca acagcacaag catcagtggt tctctgggac cccaccagc cgaccaccag 2940
aatggaatta ttcaggaata taagatctgg tgtctgggaa acgaaacgcg attccatatc 3000
aataaaacgg tggatgcagc cattcgtctc gtagtaatag gtggcttggt cctcggaatt 3060
cagtaccggg tagaagtggc agctagcaca agtgcagggg ttggagtaaa aagtgaacca 3120
cagccgataa taattggggg acgtaacgaa gttgtcatta ctgaaacaa taacagcatc 3180
actgagcaaa tcacggatgt cgtgaagcaa cgggcattta tagctggcat tggttggtgcc 3240
tgctgggtaa ttctgatggg ttttagcatc tgggtgtact ggagaagaaa gaagagaaag 3300
ggactcagca attatgtctg aacatttcaa agaggagatg gaggactaat gagcaatggg 3360
agccgtccca ggtcttctaa atgctggcga tccaattac ccatggcttg ctgattcttg 3420
gccagccacg agtttgcacg tgaacaatag caatagtggc ccaaatgaaa ttggaaattt 3480
tgggcgtgga gatgtgctgc ctccggtgcc aggccaaagg gataaaacag cgaccatgct 3540
ctcggatgga gccatttata gcagcattga cttcactacc aaaaccactt acaacagttc 3600
cagccaaata acacaggcca ccccatatgc cactacaaa atcctgcatt caaacagcat 3660
ccacgaactg gcagttgatc ttcctgatcc acagtggaaa agctcagttc aacagaagac 3720
agacctcatg ggatttgggt attcgtacc tgatcagaac aaggggaaca acggtgggaa 3780
aggtggaaaa aagaagaaaa ctaaaaattc ttogaaagcg c 3821
```

<210> 32  
<211> 1490  
<212> DNA  
<213> Mus musculus

```
<400> 32
tgaagaaat gaagacggga gaaaaacgaa gctggccatc tcatatagag cagtggactt 60
tgagtaatca gtcagttaag ataatagtta gagagttota gaaactggtt caaaatggtt 120
cgactatgag taggatgagt ggatactaaa tgtcccttgc tcccatccca ccatcccaat 180
cctacctaga gcctgctgtg gagttagaac ccagaactcc attcagggtga cagctaagtc 240
tactacgatt ggaacctctc tggttccaat gatagttctg gaaagcaaac aatgaaaaga 300
gaatogtgcc cagtgtttgc tgggtgtgag ggtcttcggc agtggggacc agatggtgag 360
```

WO 2005/005597

PCT/US2003/027106

gaacggaagc aggtctctgc atcgccaggg ttcaggttcc ttctcctggg ttgagttctg	420
tttttttttt ttttttaaat gtgaagagat tttctttgtc atttctaaaa ctctctgcag	480
ttgctggatg tcttaagctg gttgaatatg gacgtaactg taaatcccag agtgttttat	540
tttgagatga gagtttttgt acagttttata caggatatct tcttatttag acctcagggc	600
tatcttggga cccactacta agtgtgaccc ctccccgcag cttcaattct gggtagatga	660
gttacataac ttttaaatgt gatatccagc aggaagaatg tatttctctc ttttaacttc	720
gggcaaatct tgttttaaag gtctagaaaa aagacagtag aagaaaacag aggtaaaaga	780
attaaaaacc aactgtaaaa taaacattct catggtatac aattgtgcta cctgaataaa	840
cttatgtgca taaattattt aaaagtgtct tgaacatat ggtattttcc tgtcatttgt	900
ttgggttgtg gtggttttat tcatttgatt tccacatatt tgcactttat ttttcaaagc	960
taaggggccct tctagtctgt atccaccctc tccaggaggg gaggaccctc ggacaaaatg	1020
tacctctgtt tccctgtgta tctctttatg agtggcacgc catatgcgct ttcaccagg	1080
gottttcttc ccccatcaat taaaatgtcc ttgagattta aaaataattg gaaatatatt	1140
tttatattta ttgtgcgtgt gtgtgtgtgt gtgtgtgtgt gtgtgagaga gagagagaga	1200
gagagagaga gagagagaga gagagaacat gctggtgtgt tagtgtagtg gggtaaagga	1260
cggctgtaga agctggcccc ctccctccac cacatatata ctagggatca aactcaagtc	1320
gtcaggctta gcagcaagcg ccttgaccac agagtcatgt caccagtcta aagatgtagt	1380
tcagggtgac ctcaaagttg tgatctctct gctctgcct cttgagcata tctctcttgc	1440
atgcaccacc acaattgact taaaatattt taaaatcag ttttaatggc	1490

<210> 33

<211> 2185

<212> DNA

<213> Mus musculus

<400> 33

ggctgctgct gctgctgctg ctgctgctgg agcaaatgaa gaactctttt tcttaagcag	60
ataaccagct tctggcagtt gcatgatctt gctattgaag tggaccttgg taaaagtgc	120
tggtatcact ccatatttgc ctgtcccatc cttcgtcagc aaacaacaga taacaatcca	180
cccatgaaat tgggtttgtg tcatattata tcaagagacg cctgaataa aatgtttaat	240
ggtagcaaat taaaatgtcc atattgacca atggaacaga gtccaggaga tgccaaacag	300

WO 2005/05597

PCT/US2003/027106

atatttttct gaagaatgag tttgtttgca atttgtaagt gaaactgaat tatgggtaca	360
ttcaagacaa gagtgttcca ttgactgcag ctatccaagg accgcctgtt cataagctat	420
gctccagagg ctgcgcattc actcgtgtgc acggaggggg tgctccagat gggaatcaca	480
caggggcttc ttcaactctg gtcttcgttt ctgatcaagt aaacaccagc agttgtcatt	540
cagtgcagg ttttgtactt ctatatgggt atttttttac ttaaagcag aaacagaagt	600
tgaccttctt gacatgtgtt taatattcct cctgctttta cagattctga cgttttcttg	660
ataattgtaa gcttgagagt gtttgtgaa gaacttactt tcttcttatg tatacataat	720
taaatgaaaa gtcttcatag gagtttgaca aaatgaattg tggttataaa acgaatttgc	780
ttttttgtg ttttgttttt cttttttggc ctaaggaaga aagctgtgat aaatttcaaa	840
tttgcatagc ttttcaatgt tttgctctgc tcccgcctt gcttcagagt cggcacactc	900
acctgcattt gagttctgtc tatagcccag caggctgcct gtttaaaatc ccatcatgaa	960
tttaacaggc tgatgtgaga atgaataga tattactggg gttttgttgt tgtttgttta	1020
tttgttttgc ttttattacc aagaggtgct ttttaataaa tggatattga agttagggtg	1080
ttactaattt gatgtatggt ttcacagtct agcactactgt cctttgacat ctgcctttaa	1140
gacttggctg agtgtctcat tagtttatca tcacagatac gcagtgttat gcatgtgtat	1200
agaagtgtgt gcaccagcat caaacattgt gtgtgtggaa gggaaagaagc ctgtccattc	1260
taaacgcagt tgccagcttc atcacttcag gtcttaacgg gcaggctcta gcaactttcc	1320
gtgtatggac ctggtttttt gctgttttgt gtttaattag tatattgttc atgcctctct	1380
tctgcagtgt ctcatctcat agactgtgaa cctgtatatatt attcaaatgg ctacagataa	1440
tgctcttttc ttttgtgagg tctcttcatt taatgcactg ccagaaaaga gccatgtgta	1500
agagttgttc tctgttttag gaactaacta catggaaaag acttctgact taaacccatg	1560
aaatacttca tcttgagaag agtgctatgt ggaaatcacc aaatatctcg caactttatt	1620
tcatctgggt taaatctgaa catcaacata ggaaaaactgt catgagaaaa tgaaaaagca	1680
taaacacaga agcaacgaga aatgtgactc ttgttatttt aaaccacaga cggacttggg	1740
ttaggggaaat ggggacgaca gctttgtgtc taagttaatc agaaattgag agcatgcaca	1800
gtgggtatgcc agcctgggtg atgcttttct agggagagcg gtatttgctt gtaagggaaa	1860
gaatggtatt gtagaaaaac ccaagaaatg accacgtggg cagtttcatg gtgatggcta	1920

**PCT/US2003/027106**

```
<210> 34
<211> 3598
<212> DNA
<213> Mus musculus
```

60/186

WO 2005/005597

PCT/US2003/027106

cttgtttcct cctgagcctc tgtgtgccc gtagccacat ctgtacac tgcatcaggt	1140
tcagtggttg gtctttcccc caggttacgc tagtccagcg tcatgagttg aatgtgatcc	1200
gtggtgatat ctctacaga cattcaggtt ttctttcctt gttacctgcc tctgttcact	1260
tgtttaactc ttcttgtcta ttacccccca ggctctgccc caccccaact ctattctggg	1320
gactaatccc ctggcccgct ttaggcctgc tgggaaggtg cctagcactg agctaacccc	1380
tcagctcctg ggtttggctc ccttgtttca gtgtttgcta aaccttttc cacccttctc	1440
accagtcctc accttttgtt ttcaaagcct tgctccatac ttgtagctgt ttgtttttct	1500
tcagtgtttt tccaagtcct aaaattgtta gtacttttaa ttaaattgtg tggatgctat	1560
aaataaattt gataagtacc aacatttact taaagtacac caatagttaa acattgggac	1620
aaaattcagc cctcatcctt caaatcagaa atcctctttg gtatgcctt atacgttcac	1680
aggtcacgt gtggctggcg tcagctgccc ctgattgtgg gaagcattag atcctgtcct	1740
gaaggagtct gggtaccgc ttagtgctct ctggcctaaa tgtttctagc ctgtattcct	1800
gggtaaacat tcagaatgac attgccaagc acaggctaag ttacaccact ggagtacctt	1860
tgcaaataga aatgtcctat caaagatgac accggtgac aaagagttgg gactaggaat	1920
tttagccagg aattaaatct cagcctcggt gtgctaatta aataactggg gggcgggggg	1980
cttgaggggg tgagcaagtc ctgtctgtgg aagctgacta gtaaatatgg cacttaattc	2040
tgccaatggt caggtcaagc aatttaaggc agttagcata ttttgaaagt agggaactgt	2100
tgttttggtt tgagacacgg tctcacttta tagcccaagg ttggcctgga actcattttg	2160
tagtctagtc ggtctctcaa ctcaaggcag tcctcctgcc ttaaccttc aagtgtctgg	2220
attatagacc taaaccgtag tgtccagata ctgctcagtt ttaatatgata cactataggg	2280
aggaatgctc caaaaaagat tcactctgta ataactgtag catagttcag gtcacccggc	2340
ctgggtgate tcagctcctt cactcagggg cgagggctag ctacgttcct ctgccctggc	2400
tgtgatagta ctgggtagag cagcagctct caacctgtgg gtcacatgac agatgtctgc	2460
attatgatgc gtaacagtag caacattgca gtcttgaagt agcaacaaaa taactcgtgg	2520
tgtctcagtc aggaactgtg ttaagggctc cggcgttagg aaggtatctg ttgaggattg	2580
tgtcttctc togccctgat gttgtctttg ctccctggc tcccccttct cgccttctct	2640
cctcttatgt ctggcagcat ttctctactg aaggaaactgt caacatgaac ctctctctct	2700



WO 2005/005597

PCT/US2003/027106

```

cactcactct cattctctct ctctctctct ctctctctct ctctctctct ctctctgtct 2760
ctctctctct gtctctgtct tgcacacaca cacacaaaat gacaaactct tcccccccca 2820
tccaaaaaga aatctacctg tatttcaaca atagattaat gctgaaattt tgactcatac 2880
aaactaagggt ttttttctta aactcgtaga ttattaattt gaataacgta cagagaattt 2940
taagtttgct taagatctct ttggataaga acacctatta aaaaatattt gagggggctg 3000
gtgagatggc tcagagggtt agagcaccog actgttcttc caaagggtcca gagttcaaat 3060
cccagcaacc acatgggtgc tcacaacatc cgttaacgag atctgactcc ctcttctgga 3120
gtgtttgaag acagctacaa tgtacttaca tataataaat aaataaatct ttaaaaaaaa 3180
atatttgagg actagagttt tgtcacaaag ataaaactcc aaccgccttc acattacttc 3240
cttctggacg tggaaagctg gtaaacagga gagttacttc ctctctgtaa aatgtttgta 3300
ctggagatgt tgaaggccca gctctgtgtt ctccaggactg taaattatct aagcattttg 3360
atggattggg ctggcttaat ttctctctcc tagttaaaaa gaaatgcagt tgtttacatc 3420
ttgctgtgag ctaatcttaa aagagagccc tgtttcactc aggtcttcag ggcacgtgtg 3480
ctacagaatt ttttggaat gtgtgacttg cgcgaagctt ggtggtagag cacttgccca 3540
gaatgtgtga agaagctcgt tgtgtgtgtt taaaatgtac tttttaataa aacttttt 3598

```

<210> 35  
 <211> 4153  
 <212> DNA  
 <213> Mus musculus

```

<400> 35
gatcagaaat tcaaagccag cctgagctag atagtaaaag gtttgttttt ttttttttaa 60
gttaaaaaata ttttaaatata ttctgttaa ataaataaaa ttttaaaacg taaaaattca 120
cagcccaaaa ttgtatatat ggaatggggg tgattacata cctctaattt tgcattgaca 180
gaacaagacc gatggggaaa aaaaaatata tctagaatta aacttcaccc agaaggatgg 240
tgggccaatg taatagtctc ttctctctcc agtgtagtcc cagtcagggt ctaaacagta 300
tgggtgtgtc ctctgtgtct cttacaggaa agcagcaggg cagaaaaagt caacatcagc 360
cttgctctct tcctgtatga cctcctgtca atcatggaca gaggcttcgt gttcaacctc 420
atcaagcatt actgcagcca gctgtcagcc aagctgaata tctttccaac gtcctctccc 480
atgcggctgg aattcctgag gatcctctgc agccatgagc actacctcaa cttgaacctc 540

```

WO 2005/05597

PCT/US2003/027106

ctcttcacga ataccgacac cgcaccagca tctccctgcc cctccatc cctccaggta	600
gtctgctaac tacaggaaaag ggcgagctg ctttgtaat tagcttagtt caatggggca	660
tctcctatct tactaattag aggaaaatca cactattcaa accagatcag ttgatccaga	720
tatgggctct acggttcctt gaagctgcag catctaaatt gaccattttc aaatcaagta	780
atttgccaca agggtcctta aggaggttaa ctatgtagga agaatctgt aagcctagga	840
aaatgaagaa acacagggtta agtctcaagt cctccactgt cgacataaac caattattgt	900
acaatatagt gtgcaaatac aggttttagta tatttgcaa tacagggttg caatgtctag	960
caagattcag aagcactgtg tttagcctagt ctctttgtcc gacagcttac aaaggaagaa	1020
ctgcagaggg ggaagggggcac gagatgaaat gattcccaat aggatttgac tgtggcaaat	1080
gtccttactg cgtcgccacc agagggtttt caaggagtta gtgtcctcta gaaaaccctt	1140
aaagaaatgt tattttatag cctaatacca gatgtgggaa acaaggcaga tgttgacagc	1200
agtaggcaag atagctcagg atggtattag attctattct gctgcatac cttgtgacta	1260
gtacagaggg aaagcgttga cagtataag cgccctaaat tccaggacta agaggacggg	1320
ggtggggatc acatggggcc aggagtttag tccagatcag cctgagcatt atagtgaagc	1380
ctcatattaa aataataata ataataataa gtcatactag tagctatttg tgcctgacaa	1440
tatacctgaa gttagctcca tgaccattat aatgtgatct gggacacacg tgacttacia	1500
ggaccaattc caaatggact tattattgtc tgctgtcgtc tgttctgtgg gctgaatcct	1560
ataacttccc catgctgacc ttgccctggg tccctctccc atgctcctct tctggctgcc	1620
ctaaagagtt gacagaccga gggccctcac tccacagagc tccaggactt gcagggacac	1680
ttacttctgt ccccggtgaa ggaatgcacg ctcccgaggt aagaacaagg gacagggaatg	1740
gcctagggct gccaaactctg gcaattgtct agcagacacc acttctgggtt ccaggccagc	1800
taacatccag acactgtgct cagatgacct tcagaaagga ttctggggag acagaccaca	1860
gcgagggact ggttacagtc ctattttctc tgtccacgtg taccctgggc tgttcacatg	1920
caacttttaa taccagacag gcaagggagg gattagctag ttttctttgt tctgtttttc	1980
ccattttgct gttctgggga cctggtcata tcaggcacat ttcccaccac taagcttgac	2040
ccctagccta gttttcatag tcatgttcat gttggccagt cagtgcacgc gccctccggc	2100
cagagctccg taaatgcaag ccagcactgt ttaattcca gctcttcata ctcataaagc	2160

WO 2005/005597

PCT/US2003/027106

tgccgttggt atttctgtag aactcgagtt cctgtccag ttccaggac caaaagattg 2220  
ccagcatggt cgaatcgacc ccggagtacc ggcagcagca ctcccttaca gggctgctct 2280  
tcacggagct ggcgtgtgcc ctggatgctg agggggatgg gtgagtatct gacgcctaaa 2340  
atggaacctg aagggaaga tgtaacagc attccagtt caacttctta tgtgtacagc 2400  
aagacctcag aactgtacca cttaccagtt ccaagaagaa gcaactcgtt ctaagaagaag 2460  
tggtactggg ggagtataga gaggcaaggt gattagaaga tccatgaaat gggcttcttt 2520  
ttacagcact ggcagttgaa ctgagagcct ctccactgt aggccagtac tgtatcaatg 2580  
agccacattc ccagcccaa atgtctattg tttgtttgtt ttttatttct gtgacagttt 2640  
ctctgtgtag tcctggctat cctagaactc actctgtaga ccaggcttgc ctcaactca 2700  
gaaatctgcc tgcccttgcc ttccaagtc tagaattaat ggtgtgcacc accaccatac 2760  
ctgcctcaga aagaggtttt gttttgtttt gttttgtttt gttttgtttt gttttgtttt 2820  
gtttttgttt gtttttcgag acagggtttc tctgtatagc cctggctgtc ctggaactca 2880  
ctttgtagac caggctggcc tcgaacttag aaatctgcct gcctctgcct ccgagtgct 2940  
gggattaaag gcgtgtgcc ccaagcccg ctcagaaaga ctttttaaag tcccttgttt 3000  
gagcagaatt tgcagagaat gctttgctga gtgaattccc taagggcaaa cccattttgc 3060  
aggggaggct gctgagggtg aaccagggc ttgcacaca ctaagcaggc gtcctccac 3120  
taagctatcc cgtcagccct aacaaggcca cctctgacaa agtgagcaca gagacgaat 3180  
aaataccagc atgccactgt ccgaggctgg caaagggaag gacggtgaa ggcacagctg 3240  
tcctgggtct agatgacgct tcctatgggc aagccttctc aggcacaggc agatgccata 3300  
ggcatgggtc tcgtgaatct ctccactgtg tccatccctg agcacctgag tgtatggcag 3360  
tgcccgagct tactttgttg ctcttggtt gtattctgtc atcttttctc tgctctaacg 3420  
acattccagt cttctcagaa tttctgtcc tataactaac ttattttctc agcatcaaaa 3480  
agtgccctag gatatatgct gataaggctc tgaaagaaga aaatttgctt tgcataataa 3540  
acaaccccc attttcaact tttaattgt ttttaataaa tagcatggct ttaagtaatt 3600  
tctgaaacta tcttttatat acacagtagc agtagttttt aattttctat ttttgcoca 3660  
gttgagagaca tcctgccgt ctggttttga ttctctaaa atcattgctg ggaattgct 3720  
atatagcttt agctgttccg ggcttacta tgcaaaactag actggcctca aacttacaga 3780

WO 2005/05597

PCT/US2003/027106

gatctgctgt cctctgcctc cccccaccac caccoccagt actggagtta gaggcatgtg 3840  
ccaccatgct gagctcctaa tatttttgaa gagcaaaagg ttgaaataga cattttccaa 3900  
agaatgcgtg gtcaaaagca cacaaaaaag gtgtccagaa tctctaacag tcaggcgatg 3960  
cttcattaaa acaatgatta tataccacat tctgctact agaatagttt gatcaacaag 4020  
acagacaggc cagggatgtg gctcagtggt agatctctag catgtgctaa ggtctgggtt 4080  
ccatccccag cactttaaaa aaaaaaaaaa agaaagaaaa gaaaagaaaa gaaagaaaga 4140  
aaaaagatgg ttg 4153

<210> 36  
<211> 3009  
<212> DNA  
<213> Mus musculus

<400> 36  
atagcaacaa caggagcctg tagcaagagc aggagccaca tgggcctctgt tgcacagagc 60  
tcagagaagg cgatgatgcc catgccaggg taggaagcaa ggagttgaa gtttaatggc 120  
gcatcttgga gatgcggcgt gactcctggc cgaggtcttg ttcttctcct agcccaagtg 180  
gggaagctct ctctgccatc cttctgcctt ggctataccg aggatgcgca agagtctggt 240  
gtctctctag aggactctcc tgttactgtc ttcccccctt gctgttcttc acatgaaatg 300  
atgataataa agtaaaatca cgtcagtcca aacgtcacag ttttaagtt caaatgact 360  
tcccaagtgt ggctgcagcgc tctctgccc gatcggtcgg aacaggttct cacgtgatcg 420  
tggggagggtt cattctgagc cgctagtccc gccgagactt tatgtctatc aggaaactgt 480  
gttctctgga aaggattatc ctgctggctg tctacctct ctgttaagtg gcggcccgat 540  
gccgtggact ggtgtgattt tattgcaact ttaatcatta tcatgggtga agctgccgta 600  
gatggtgtaa agtggtctgg tccccttcg ttctgtctgc acagggttac aataaataag 660  
ccagtgggtg gacaggaagg gactctttat ccagaatgg ggttcagcct ggagcaccat 720  
caccagctt cttagcggag cctcgggtgt ggccggatct cctctgggat ctctctatct 780  
tcactgtcac cctgggaatt aaggacagct atgctctgct ttgagcaagc ttcccagccc 840  
caccttttct ctctgcttgc ctccctgcct cgctccctgc cgggggagtg gcctcgttgg 900  
ctctggggcac ccagctctct tcccctagca tccctgtctc cctattcact cccctgttca 960

WO 2005/005597

PCT/US2003/027106

tttttgtttc cagtgaagtg tgccaccccc agccctccca cctccctgc ttccccgatt	1020
ccaccagtca accccctctc gtctgacgc ccacggggcg ccgacagcag ccataccatg	1080
cgggtctgag ctctgactgc aagccctggc tgaggccaat gctgtgaagc tccacagagc	1140
caccttctga tagcatccat tgcacacctg gggctctggc ttctaccctt ggcctcctgc	1200
ccttccaccc accatgggaa cacgtcagag agccaggctg gggacggggg ctgcttcata	1260
aaggaacatg gatgccttca agttcacatc tgctgccctt tcctgaaagc ctggcactgt	1320
cattttatgg ttttaaggca agaccggggc atggcaaggc caggatggcg tctctctga	1380
tgccccgtgc acggggagct caagtgcagt tctggatgga ttgtgtggcc ctctctgacc	1440
atccccctg gtgctccatg gctgggtggga agctcatgct atgggtgagg gctagaagtg	1500
aagacaagac agactccatc ccttggaacc cgtacaacac agcgagaggc caggctcttc	1560
catcaccttc ctccatttca gtcccagctg cctcagcgat gcccaaggct ttggcacggc	1620
tctgtctgat ggtttcccag agttcactgg aggcoagcta cctgtctga gccaaagaag	1680
acgatgagtt ctaggagag gctcctgggc tccagagggg gtcaagtgtg tgacagagag	1740
acgacagcag gtctgcacag tgtctgaggg caagtggaa gcaaggagca agatggaaga	1800
gaaaagaggc tttagagagt aagggaagaga aggcagacgc ttttcacaag caacagggat	1860
gtaaagaagg agggaaatgg gaaggagaga tagaaatggc ttccctagtg tggagcctta	1920
ggtcagtgcc aagcagaggg gctgtcacct ctgtaccttc acgtcttctt cgggagcagg	1980
aggcgccagg aggactcatg ccaggcacat gccagctcca actgaggctg ttggtagcaa	2040
ggtatgaggt aaggggttgt tagagtgtca tagcctgtga gatggtccta tctgtgtcaa	2100
ggcctgctgt ctctctccca gggtcatagg cagagagaag acggtctcat atgaagtctg	2160
tcagccttgg ggccctacct agccagttta aaccggaaa gtactgtggg ctgactgagg	2220
tttgccctcg gaggaggaat gaggaattaa ctgtgaggcc aagtcttagg tccttccttc	2280
tcctctcagg catttagagc agggccagat gctttcctcc accccacctg cccagggagg	2340
acaggacagg gagagacct agcagagcag aatcttcctt tagcccacct accgtgctgt	2400
aatgtagcca gacagcagca aagggaaggc agcttcagac accaagccac cagacctggc	2460
tctccacaca tttttgccca gagacttcag cctgaacatc agtggccagg gaaacaactg	2520
catcagctcc catcaatcca tcaccactcc gtcatgggtc gggacagtta ctggttcata	2580

WO 2005/005597

PCT/US2003/027106

tgcaagtaaa gatgacaatt ctttcaacaa aaattagtga agcactctct gtgtatcagg	2640
cactgttcta ggtgcttagg atattgtctt gcttctgagg gactctggat cgggaggatt	2700
ccacctgttt ttgcctctct ctggcttctg gaaagtgtct ctcatgaca tccccatatc	2760
gcatagtcca agcaccacaa atctgccctt tctccttaa agactggtag atgggatcag	2820
ctcccagggt accctctctc cccataccct cttccaaaag aaacaaaatg ttagggcttt	2880
ccccgtcgtt gtctctcctt tttttaaaaa gtggtatttt ttagaaatc atgtggaata	2940
ccaagaaatg tctttgcctc cccaccactc tcactacat ttcataaagc tggctcttta	3000
tggtgcttt	3009

<210> 37

<211> 1599

<212> DNA

<213> Mus musculus

<400> 37

gagaagcatt tgcattgcaga gttggggatg gggcacagag gggagagacg agaacagtca	60
gtcgggtggg tgcagtctgg aagagtgtct tctaggaaca cagaagtaat tagcaggaga	120
aacagctgca ggatttaaga ttggattttc cgagaggatg aaattggttt tgaagtaaag	180
gtggatccag cttttgtgtt tgacctttac cctgtggaat aacttgattt ttctaagctg	240
caagctgttc gaaacctctt ttgcccac agtggtttgt ttcatattgt tttagatgg	300
gctttcactg tggcgaccca tgcctctggc ctccgtggaa cagctccggc cttagcctct	360
caagtgtctg gattacaaca tgtaccacac caggcccac tcgcagactt ggagtaaact	420
accaagtctt aggagccctg acacagatgc catctgccac aggcattctc ccttctgcct	480
ttgtccttcc cggctgagct ccagattgta gaagacatct aaggttcag tatgactcca	540
tcattggcaa attcaatggc acagtcaagg ccgagaatgg gaagcttgtc atcaacagga	600
agcccatcac catcttcag gagcgagacc cctctaaccat caaatgggac gatctgtgta	660
ctgagtatgt catggagtct actggcatct tcaccacat ggggaaggcc gggggcccac	720
ttgaaggggt gagccaaaag ggtcatctc tcggccctt ctgcccagtc ccccatgttt	780
gtgatgggtg tgaaccagga gaaatatgac atttcaactca aggttgtcag cactgcatcc	840
tgcaccacca actgcttagc cccctggcc aaggcatcc atgacaactt tggcattgtg	900
gaagggtcca tgacctgggt ccattgccac actgccactc aggagaccgt gaatggcccc	960

WO 2005/005597

PCT/US2003/027106

tctggaagc tgtggtgtga tggccatggg gctgccaaa acatcatccc tgcattccact	1020
ggtgctgcc aagctgtggg caaggtcatc ccagagctga atgggaagct cactggcatc	1080
accttccatg ttctacccc caatatgtct actgtggatc tgacacgtct cctggagaaa	1140
cctgccaaat atgatgacta gaaggcagtg aagcaggcat ctgagggccc actgaaggac	1200
atctcgggct aaattgatga ccagggtgtc tctgttaact tcaacagcaa ctcacactct	1260
tccacctttg atgctggggc tggcattgct ctcaatgata actttgtaaa gctcatttcc	1320
tggtatgaca gtgaatatgg ctacagcaac aggggtgatg acctcatggc ctatgtggcc	1380
tccaaggagt aagaaacctt ggaccacca ccctagcaag gacactgaga gcaagagaga	1440
ggccctcagt tgcctgaggag tccatatccc aactaggggc acccaacact gagcatctcc	1500
ctcacagttt ccatcccaga ccccataat aacaggaggg gcctaggagc cctccctact	1560
ctcttgaatg ccatcaataa agttcactgc aaccaccc	1599

<210> 38

<211> 2627

<212> DNA

<213> Mus musculus

<400> 38

gagctgggga aaaccaagta ctattattct gttaaaggaa cataggcatt gtggtgtatt	60
caaaaataag ggccatgctc agctatcatc agagatgttc ctgcaacagt gcaagaaata	120
aatacacagt cccacagcca ggtattgtgt agagagtgat atgcatagag ttgcaagga	180
tctgcacctg aaaggggtcc cattgttgag agaagtagac acatgcctcc agccttaaac	240
aagaagctat caccaatgac cacttaaaaa tgaagatttt ttaccacct gtagctcaa	300
taaggataaa aacccctctt aaagacagcc cctatgccta gtaatagaga tggccaacac	360
aaaatgaact caatgacatc ttggatatt atttgcata ggtttttcca agtcaatttt	420
ttaacctttt aggacttttg aatatatatt atttccaagt catttttatg ttattcttgt	480
ggctacaag gtatacaact ctgcatttat atgattttct ttggatcatt ttctatgttt	540
tttttctgtt ttccattggt ttgatatttt tctttatctt attttatttt atatatatat	600
tttaagattc ttgttgtgtc tcttacaaga aacaggcagg ggaatgaatc tttttttttg	660
ttttttttgt tttttttttt ttgttttttg agatagggtt tctctgtata gccttgcta	720

WO 2005/005597

PCT/US2003/027106

ccttggaact cactttgtag accaggctgc cctggaactc agaaatctgc ctgcctctgc	780
ttcctgagtg ctgggattaa aggtgtgtgc catcacacac ggctgggatg aatcttaatg	840
gaagttgtat aaggggaac cactactcaa attggtttta ttttaaaat atctatttta	900
aatctaagaa aaataggaca gaatttctaa ttctctgtga aattggcttg aacatatttc	960
tgctatttta aatatattct cagctactct gattacaaaa ttattatatc attcaacogt	1020
gatgtttttg aaaagcttgg ggtctacogt atcaaatatt tagctaactc ttaatttcct	1080
tataaaaataa gaacctctgt atctttagta ttcaaatgg tttttgtctt aaacataaaa	1140
tttatttttaa aataacttta tacttactat cagtaatttt atttttatgc catttacata	1200
ttttaaact tgctacagta taaaattttc ttgtgtatac aggattgtaa atagaactgc	1260
ttttaattta aaaaaaaaa gaatgtcact taagattgaa tctgatata caaaagaaaa	1320
tttgaacatc ttgaaatta gcattaatgt caatcagatt ggaaactcaa aatttaattg	1380
cgaatagttc ctaaactgac tgaaaatacc ttcaaaccat atccagaaaa gtgctcttta	1440
acagtaagca tgaaacgaag actagaaaaa ataaagtctc tacaatgtat taaaatcatg	1500
cagctacaaa tcttatttac tttaaagatc tatgaataac aacaacaaca accaaaatgt	1560
caccatgacc tgaatgttc agtaatagca tgtatgccta tatggtaacc aacagcgttc	1620
ttactggact tattaccac actgtggaga tgaggggaga tcatgcctgg aatcagaaac	1680
ctgtgagagt gtccaacat actgaaatca aggataagaa tgcaactatg tcaattatta	1740
aaccaacaaa atctctaact aaattctaaa tgtttgtcat tatgtgtac atagataaga	1800
gaagtctca ttactcatca agaaattttt ctgtgcagca aatgaagata tttaaacac	1860
caattgaaat ttgagttgt gaggccaatt tccaatgtg tatatatcca taactcctat	1920
acttaaggct taggaagcat tggcaaaagg acacagaaac ctggagtttg ctgtaagact	1980
atgattttcca gaaatgtgag aatttgacg tatggagtct caccaaggct tccaaaatgt	2040
tgctggaact gtgataaagg caatagacat actaacatca agcagcaaaa tctcatgacc	2100
cctcaaatct agacaaagaa atacagatac ctaaagaata ccgagaacag gagaaatagt	2160
ctacctcaaa gaaagcaga ttaattgggtg atccaataac gacagttcag gtctgaaac	2220
atacaagaaa cagtactcag aaccaggctc tatttatgta attaggagtg ttcacatgca	2280
tgcattgtgca tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg gtgtattttt	2340



WO 2005/005597

PCT/US2003/027106

tgtatatgta tgtatatgca tattttaga tgcattgtgt tgtatgtgtg tatgtgctag	2400
atacagatag ctatgtcaca gcaattaaag aaagtcata atttgaaaag ggggggagat	2460
ataaatgaaa ggggaatgaga aagtgtatga attatattat aattttgaac tgaataatct	2520
tctaatttca aaccctgcca tatatatgta agttcaaat ctacttttt caatttaaat	2580
ctacctcaat gccagctgtc tctgtctttg tctttgtttc cttatcc	2627

<210> 39

<211> 1854

<212> DNA

<213> Mus musculus

<400> 39

tcaaaactaa ctccctgagc tgaccaggaa agatgccctt gacgagcatt gcagttttta	60
cagcacagac aaccagaaa cgtacatact gctaaagtgt atggctgtcc cagcatctct	120
ctctccagcc agctctcaga gctgcccaga gcttcaacac cttgaacctt atgtgcttag	180
gagtgcagct agtcaggata gccacgagg cagctgggta tactttatct agggcacttt	240
ctgtacatgt ggggttagtc tttatatgta ggagattatt aaatgccctt ttgctgtctc	300
ataataattg cagatacctc atctttgttt cctactactc ttctttgtag aggggcctga	360
tggcctctgg ccctcctcta tcaataattc atgattcctt ccctgtcttc tgtctttcct	420
ttctgcgga cgttctctca accctccctc ttcattctac acattgtagt gggggcaaat	480
ttttacttga gagatacgt catagtatgc agtttatcct tgtacagtgt acatttgatt	540
gtcgtctatt tacagagctg tggaaccatt atcatcatca gttttagaac atatttatca	600
ccagaaaaat cctgttccca ctgacagtc ccttcacct ctctcagac ctggcaacta	660
ctaatacttc tgccttctgt gatttgccca taacggacct ttcaataatg ttatatgcga	720
tgtgcaatgt gtctgtttac ttatgtttta ggttcatctg tgccatggta tatatcatca	780
tttcaagtag tgagtacctc tctctctctc tctctcttc tctctctctc tgtgtgtgtg	840
tgtgtgtgtg tgtgtgtgtg tgcgctgtgt cgcttagaca ttttcattgt gtggccctgg	900
ctgcccttag aacaggctgg tcttgagttc acagaggag ctctgcttcc cagggtctgg	960
gattaaaggt gtgtggcact gtgcctgcca gtgggtttgt tttgttttgt cttttctctt	1020
cagtttttta aattgtctaa atatttcatt acagtgcata taatggcggt tctgtgattt	1080
ctagtcagga cgatcatgaa taggcttctg tatatatgtg tgtgcaacac ccctcatgt	1140

WO 2005/005597

PCT/US2003/027106

tctccttcat	ggacatgtgg	gggttttgg	ggtggtggag	gtgggttttt	gtttgtttgt	1200
ttgtttttgt	ttttgagaca	gggtttccct	gtgtaacaag	ctctgtctgt	cctggactca	1260
attttagtac	cagggcctgg	gcctcgaact	cacagagacc	ctcctgcctc	tgctagccaa	1320
gtgctgggat	taaaggggtg	caccaccaca	ccagcgtgt	tttcattctt	ttgtatagga	1380
atagaatgga	tggatcgtaa	ggcagctctt	acctttagtc	tttgaggaa	ttgccaaagt	1440
gtgttcccat	ggaggatatc	aggattccag	tttatcaagt	cttcaccaat	attgtttact	1500
aatttgaagt	gtgtttcatt	gtgtatgtgc	tgtgttttat	tttgtgggca	gtgcagggga	1560
ccagaccag	gacttcgaga	tgtagacaag	tattgtacca	ctgggctcca	tcacagctcc	1620
cttagctggt	tctgagttgc	agtttcctaa	taactagtga	tgttggccat	tatgtcttcc	1680
tcttcctcct	gtgtctgtgt	ctgtggtttt	aagatagggt	ttcatgtgtt	ggacaatatt	1740
tttgttttgt	cttttttttt	ttttcaaaga	tagaatttct	caggctgggg	aaataggctt	1800
acaacaaaaa	atataagagt	tgggttccta	gcaccatag	ctgtctctcc	agcc	1854

<210> 40

<211> 3683

<212> DNA

<213> Mus musculus

<400> 40

acgattataa	actgaagaca	cttaattctg	gtagatacgt	agactcagct	gataatacca	60
atcactactg	atcaaaactca	ggatccatgt	gtgaactgta	ttcattttctc	tgtggtgctg	120
ggagtggaa	cgggatctct	gtattctagc	aagtgcctata	cctttgagcc	acacttgagc	180
cctcccacac	gtacagtctt	aagcatgctg	ctgcccacac	tgacacacag	agatgcacac	240
tgacaggcag	agtagcccca	gcaaccacaca	tacagatgtg	tgtatctaca	cagatgactg	300
agtctcacca	atgcacattc	ccaagtaact	agaacctata	agcttctgtg	atgcttgggt	360
cttaaaactcc	cccactctcc	ccggcctcag	tgacagacaat	ggggccagct	actaggcagg	420
aaactggagt	ggcaaggtag	gccaatggta	ttaaagaaac	cagacggggg	ggtggtgcac	480
acttcaaagc	ctagctctag	gaagacagag	gcaggtggat	ctctaggcta	gccttggctg	540
cagaatgagt	tcacagaacg	ttaggggggac	ctaaacaaac	cctgtatcta	aaaacaagag	600
ctatatccag	ttgtctgctg	cattgggcag	gtgccagctc	cacatacacc	tccatggcag	660

WO 2005/005597

PCT/US2003/027106

tgggcacacc ttctcttcc tctagggaca gcgactcaga cttgtacagt taccagcccc	720
agagctgtct ctctgcttca taagatgtca ctctcattt ttaggggtga gaaaatgggg	780
aagaatatat aggctgtaga caggataagg agttgagcca aggccagggt ccctccactt	840
tcctcgtgtg gctgttttg cacaagtgtg agtatctaga cttgcaaaga tactgtctct	900
caacaggagt ctgggatgta agagacaggg actgggggct ggagaagtgg ctcagggtt	960
aagagcactt attgtcttct ccaaggatct gggctctatt cacagtacct coagggtagc	1020
ttaccaccat ctgttaactc caattccatg gggatctgac gcctcttct gatctgtggg	1080
caccagggtg gcaaaacatt taaaataaa ttaagtctt tttaaaagta actttaaaag	1140
tcgtttattt ttatttcatg cgtattattg gtgctttgct tgcgtgtatg tctgggtgag	1200
gatgtccgat ttctggaac aggagttaca gacagtgtt agctgccatg tggttgtctg	1260
gagttgaacc agagctctgc aagagcagcc agtgctctta accacagagc catctctcca	1320
ttccaagtca ttgcatTTTT aaagagttca aagaaagaag gtgggatggt aggtaggtag	1380
tgagcctctg cagtggggta aagtcagatc aggaactggt tttgtggagc atgcccacct	1440
ggctcagttg ccctctgct gactcctccg tccatgctcc atctatgctt atctttgggt	1500
tgctgtgttt gcttctacag atggggaggt tgctgactg tctaccatc ggctgggacc	1560
ccagagccaa gccagctgag tgagtgccga gggccccagg tgaccggggg agtggcactg	1620
ctcaggcctc tgcaaagact accctggaga agctgatgct ggtggagaca gcccttctt	1680
gctgagtcca gcctctgcag agcctgogca ggttaactgt agccagtgt acaagatcg	1740
cctcttagct taggcagaga gagagacatt aatctagcct attogaactc cccattatcc	1800
agagaaggga atagaggctc atgtggcaca gtgagtcct tagcatcctg cctcctagcc	1860
tgaggactct tccctatgcc tccatgacct ggagaactgg gcggagagat gggttgtgac	1920
ggtgaccagg attcagggca gaggtggaag ccagcgtgcc tgatatatgc agctgacctc	1980
cccaggatc ctctacagag ctgagaggcc atggtagtcc aggtgtgatt gcatgcccgg	2040
cagctggccg cagggcaggc catggcagga cccatcttct ttgtggcca ggtttagccc	2100
accaggctc ccagccacag aggccagggt gggctgcct gccctataga ggcaactccc	2160
tgaactgaca catgaagcct caggctccag gaagctcett agagtttagc ctgctggaaa	2220
cccacccaa cttccaaagg agcatttctg aggtctgcat ggggggtggg cctccaggga	2280

WO 2005/005597

PCT/US2003/027106

tggggaaggggt ggggaggcgag ggctgcaggga ggatgtgagg ctgtaaatgt gctgtgctgg	2340
gtctgtgtgc aagcagggtgt gtggggctct ctgtccttag tgcaacagggt tgtgtatgca	2400
agagttacat aagtggccta tgtgggggga atagttaaga gcttcacatg tgtgtctgtag	2460
tggtgactgc tggctatgga tcctatgcag gtgtgggtat cctgggctgt ctaccacaca	2520
gggtactagt ggaccaagac tcaaacaccc ttgggtgggt ttgtgtgtgc tcagggttct	2580
gagcacaagg tgagggtggc tgtgcacatg gctccctttg tgttttgag gtgggctggg	2640
caggacttgg gctgcgttgg gctcagcaat gccagcctt gtggccaaac tgcgtgaagtc	2700
acttcctttt caacagtgc tttccagggg gaggagtctt tccgacctgg tcggcagtgga	2760
ggggcgctggc cgaactggct ctctctgggg agggatgtgg gcggggggcg gagagagtg	2820
ggaggagtg ttagtggtac tggaaagggg agtcctctgg gagacagaag gaaagacaag	2880
gacaggagtc tggaaaggcc aaggggcagg ggaatgggg gtggagtggg gctgaaagca	2940
cagtcctctgg gtgacctcg agggagggaag ggagggtctg caatgagtg accctcggtt	3000
tcagtggagag ctggcagtg gcctacaca cctggcactc ggggcaagg gctggcagg	3060
ggcggttcag gaacagacct gcttgccagg tgccccactc tggacaggaa gagggtgggc	3120
gggggctgta caaaggagct ctgtgtggct gaggatagg taggggtggg tatgcagtgc	3180
tgtactgttc tggggttggg ggagatgatg gggggggggc aggaccagtt ccccttgggg	3240
catcagtgcc tccaggggga cactagtgg tcaggggagg tagtgcatct tgataacaaa	3300
ctgggggaaa agagattaga agtggtagt gagatagttg aggaggccag ggctagtctg	3360
aatctttgga tgatgaagca atttgactta aaggatccca acaaaaccaa acttaggtga	3420
caacaaagct gattggcatg gctgtgtgtc cttaagggca tgactaagcc tctctgtgtt	3480
cacatttaaa tgcaaaacaa gtgactgggg ctgggtgagat ggctcagcag gtaagagcac	3540
cogactgctc ttecaagggt ctagagttca aatcccagca accacatggt ggctcacaac	3600
catccctaac gagatctgac tccctcttct ggtgtgtctg aagacagcta cagtgtactt	3660
acatgtaata aataataat ctc	3683

<210> 41

<211> 2311

<212> DNA

<213> Mus musculus

WO 2005/005597

PCT/US2003/027106

```

<400> 41
aatgtgcgt tattggggtg taattgcgat tgctagcagt tttagtagg atggcagcat      60
agttgtatat atccaaggct gatacagaat ttggtaggac ttgttatgtt atctatcaat      120
gggagacaag ttgtcggaca tcaagctcag gggttatgcc tgctatgaaa ggctaccagc      180
aattgagcgc catcccgctc tgtctgtgtg tcttgtcttg tcttttctct ccttctctcc      240
ttccttctct ccttctctcc ttccttactt ccttctctcc ttcttctctt ccttctctcc      300
tctctctctc tctctctctc tctctctctc tctctctctc tctctttttt ttttcttttg      360
gttttttgag acagggtttt tctgtgtagc cctggctgtc ctggaactca cttgttagaa      420
caggctgacc tcgaactcag aaatctgcct gcctctgcct ccttagtgct gggattaaag      480
ggcgccacca cgcgccgctc atccctgtct ttcttgattg cgagatttag aacatgggct      540
taatgaagaa gttgcttagt gagataaggt acaagttata tttttaaat taaatttata      600
aaactacata atacttttga aatcatttaa tgttcaata tttttattcc ttatatctca      660
tttaagaag tatcacacag aaaagcttaa aattatacat gagattgcta taatagagtg      720
tatgagctgt agcaatttca ataaaaaga tgcttgaaaa attatgtaat gactgacctt      780
actaattgtc ataaacttca catgtcactt gtaatagggc aaaaactgcc tctattaaag      840
gttttataga aacctgcttt attgcatttt agttacagga ataattcttt tgttgggata      900
caacctccac tttgtcctct ggaagagtag agaccttgtt agatgttcag gataagaaga      960
aagatacgag atataataac tgtattgtga aagctctgtt ttagattgaa agctgcctgg      1020
aaataggtag tacagttttg ttttttcaac ttataagctt attaaaaatt cagcaaaagg      1080
agtgatacag acacacatct atctaggatc ctttttttct ttccctgggac acattcaaga      1140
gagagcagtg ggttctgaag tgccatttgg ttttgcatg cctttatttt tggctctagcc      1200
gcactgttgc ccagacttgt cttgaactca tggactgaag ccactactct gcctcagcct      1260
cttaggtgca tacatggcta cctggcgctt cttaccgtct ctgtacaag agtacttgca      1320
catataattt atattgttac agtaaggcat taatgcagtc agacctgttg ctaagggtca      1380
gggttcaga atcttacttg tgctaaatta atgtgtgttg gttggttagc ttgctggctg      1440
gctgttgttg aatttgtatc aaccttagtg ctgaaattac aaatgtgtca tcacatcgac      1500
ttaacctaat ataattgttt ttgccagtt agactattca ttttccaaag tccacttaag      1560
gactttgttg tgtatgggtc taggtagctt gccacagtat cctccctcc agattctagt      1620

```

WO 2005/005597

PCT/US2003/027106

```

catgaggagg cttcctgctg gttgttgctg cactgcatac cagtttcttt tgacagaaga 1680
gggtacacagc tttttacaat actttgataa ttgaaactat atttgcaccc ctacatttta 1740
cagggtgtgtt tgctacagac cctttgtcag ttccagcacc aattgttttt ctaaaaagtg 1800
tagtcttagt ttaatgaact tgaatttgta agatttatat aatgtatata tatcctttga 1860
atctttgatt tactgtcttc tattgattat atctattctt attagtcctt ctggaccctt 1920
ttcttatcat ggccacctcc caactttatc tcctcctcaa agtagttttt ataagaattt 1980
gtgtatgaaa aagaggcaga gaagatataa atatgccatg tgtaccacac gaggcatttg 2040
atcttcctac ttacgggcat tgtgagccac ctgatgaggo tactgggaat agaacttggt 2100
ttctctggaa gagtgggaaa tgccatggaa tcttctccag ccccttttcc tttttttttt 2160
tttctttttc cctcttgctt atggctttgt ttttgttgg ggggagtggt gatcttttcc 2220
tttacttttg taaagtgttt aaaaaaaccc atcagcattt ttctactctt tgcttccctc 2280
tttaaaactt aataaaattt ttgagaattc c 2311

```

<210> 42

<211> 2421

<212> DNA

<213> Mus musculus

<400> 42

```

tctctctctc tctctctctc tctctctctc tcttttaata ttaacaggag accaccatgg 60
acagcatcag ctatccatgt tatttacctc agtttagcca gttatttacc tcaggacaga 120
atggaagtgg gagataaga cagaggtgta gggaggagag ggagaggagc acctccgtga 180
cctcttcacc cagttacatc aagttccaga acctccagg acagtgccag cagctgcacg 240
ccaagtgttt aatacataag ccttttggga acatacttcg tatctaaatc acagtgcagc 300
atgtgctggc atacagtgtc cataacctca tctgagccta ctccccgta acctgcgaa 360
tctaaggtct tcctgttagg ccagtgggc agctcagtaa ttaatgggtc ctgatgccaa 420
ggctgacacc ttgagtttga tccccagagt acacatgggt gagggagaga cctgactttc 480
aagggtgttc tctaacttct gcatgcacat cccctcctgt cctgccocag aagtaataaa 540
agtgtgcagt aactcattag taagaaaatc aagtcocact cctcaaaatc ttttttttcc 600
tagagatttt atttatttat ttatttactt ttaaagattt atttaataata tatgaataca 660

```

WO 2005/005597

PCT/US2003/027106

ctgtagctgt cttcagacac cccagaagag ggtatccgat ttcattacag atggttgtga	720
gtcaccatgt ggttgctggg aattgaactt aggacctctg gaagagcagt cagtgcctt	780
agctgctagg ccatctctcc aattctttga aagtggatcc cccccatga gtgggttagca	840
ccatttttct gtatgcagaa tcgtggcacg gggacttaag ctgcttctaa actacaagtc	900
gtcttagctt ggcggttato ccaatcggtt cggccacacc cagggtatcc atctgtcacc	960
aagctoctga gtatcttggt gtacttgatg cttgttgga aatgggttttct tctggtcagc	1020
tgaatcattg gccacccatc tactaaactc acaatttgca aatctagggt actgttttca	1080
tcacatcttt aatttttctt tatgaatcta taccattaca caaatgtat tattttcatc	1140
ttgtggggga attcaggaga ggaatgaatt aaaatgtgtg tccagcta atctgatttac	1200
ttggacatct acattttatt gacagaaaaa acatgctgtc aaattgtttt attaaggcag	1260
ttccctccat cctggactga ctgaactaga aaacctccat caataaaaga cattgtcttt	1320
gtcataatgc ttgcagttg aacagacagc attgaataat tatggaaata aactttgatg	1380
ggctctgaga aggaaaaaaa gtctgatggg aaacatgaat attacagta tagattctac	1440
tagaatcttc caaagggcca tctcactat tggagaaact ttttagtgta acgaccacag	1500
cactcaggat accagctgtg aacagtgggt ccattaacca ccaagaggga gcacagctca	1560
gtgacaaaaa gatagaaata aaggagttg gagtccactc tcagagttct ttggcaagat	1620
aaagctgttg gcactaaatc aatacactca tcatgactgt gtcacaaact ggacaacgtg	1680
ctaggagacg gtttaattgt ttattctttt cttttttgaa tgtgtttgog tgtgtgtatg	1740
tgtgtgtgca tgtgtgtgaa tgtgtgtatg tgtgtgtgtg tgtgcatttt gtgtgtgaat	1800
tgtgggccac agaggagcag tggaggtcag atgacaaact cgggttggtc ctcacctct	1860
actgtatttg aaacaggacg tcttgtttgg tggtaacctg gtatatacac atcacactaa	1920
ctgtcatga cctcttgag catcctacct tggttctctg tctcactctg gctgcactgt	1980
cgtcacagaa tatacactac cgtgtcccca gctttccatg gcttcagctc ttaatgacac	2040
gtgtttttgc tcacogaacc ctctccccag cgtttacgac ttattcttgt atgaacaaac	2100
ttgtatctaa cacctactgc atgcacagac tacagatgct agctgttaag agttatgcaa	2160
tgacatccct catagaaacc atgcattgtc ttgtttggtt tttctgccct taacctcttg	2220
aagtgttgga tttgaaacca cagatgagat ggaatgagctg gtgagatggc tcagcaggca	2280

WO 2005/005597

PCT/US2003/027106

```
catgtgcttg tcgtcaagcc tgagatagag tccctaaaat ctgtgtggag gaagaaggcg 2340
tggaactctt aacagctgtc ttctgacacc cacatgtgta ctgtagaatg cccgtcccac 2400
ccccataaac aaataaaatg t 2421
```

```
<210> 43
<211> 2545
<212> DNA
<213> Mus musculus
```

```
<400> 43
aagcagctct tacatggcct ttctacagct ctctgatcta ctcttccct ctgtatttcc 60
tttagacagg ggccaagcct aacctctgta tatggtctct acaagttctc tctccccctt 120
gtatttcaaa taatgtcatc actgttgggt tctgggaacc tcttgcttcc ctggcatctg 180
ggactttatg gttgctatcc ccatttcacc atcccacact gctatacact tctgtttaaa 240
tttgtagccc tctgtacatc ttactgttt cctccacac ctgactctgc ccccttttgc 300
cccgacctct ctctctctc actccctccc aagtctatct cctcattcc atcttccagg 360
atggttttgt tccccctctt aagtaggact gaagcatcca cactttgatc ttctttttc 420
ttgagcttca ttggtctat gaattgtacc acgggtatcc tgagcttttt ttgtaatatc 480
cacttattag tgaatacata ccattgtgtg tcttttgtga ctgggttagc tcacacagga 540
tgataatttg tagttccatc catttgcaga atttcatgaa gtcattgttt ttaatagctg 600
agaactaatc cattgtgtaa atgtaccaag ttttctgcat ctattcctgt tgaaggacat 660
ctaggttgtt tccagattct ggctattata aataaggctg ctatgaatat agtagagcat 720
gtgtccttat tacatgttgg agcatctttt gaatatatgc ccagagtgg tatagctggg 780
tcctcagata gcagtactat gtccaatttt ctgaggaact gacaaaactga ttccagagt 840
ggttgtgcaa gcttgcacac ccaacaacaa tgaaggaatg aatgttccct tttttccaca 900
acctcactag catctgctgt cacttgogtt ttgatctta gctattctga ctagtgtaa 960
gtggaatctc aggggtgttt tgatttgcac ttctctgatg actaaggatg ttgaacattt 1020
ctttaggtga ttctatgcaa ttcaagatto ctcaagttag aaatctttgt ttagctctgt 1080
accatttttt taatagggct atttggttct ccggagtcta acttactgag ttctttgtat 1140
atatgggata ttatgcttct atcagttgta gggttggtta agatcttttc ccaatttgta 1200
ggttgccatt ttatcatatt ggcagtgtcg ttgaccttac agaagctttg caatcttaag 1260
```



WO 2005/005597

PCT/US2003/027106

```

agatccatt tgtctacagt tgatcttaga ccttaggaca ctagtgttct gctcaggaaa 1320
atttctatg cccatgtgtt cgaggctctt tctcactttt tctcctgtta gattttgtgt 1380
ttctggcttt atatggaggt tcttggtcca cctggacttg aactttgtac aaggagataa 1440
gaatggatca atttgcatTA tctacatgc agactgctac ttgagccagc accatttggt 1500
gaatatgctg tttttttttt ttccccccac tggatgattt taacttcttt gtcaagatt 1560
agatgagcat aagtgtgtgg gtttaattct gaatcttcaa ttctatttca tCGaactacc 1620
tgctttcttc tgtgccaaGA tgatgaggtt tttatgtata ttgctttgta atagagtagg 1680
gatggtgatt tccccataa gatctctggt gagaatagtt ttggatatcc tgggtttttt 1740
ttgttgttgt tgttttttca aatgaatttg agaattgctc tttttatctc tgtgaagatt 1800
tgagttggaa tttgatgggg attgcattga atctgtagat tgcttttggt aagatggcca 1860
tttttactat gttaatactg acgatccatg agcatgggag atctttccat cttttgaggt 1920
cttctttgat gtcttttttg ggagactaga agtctctatc atacagatct ttcacttget 1980
ttgttagaat cacaccaagg tattttatat tacttgtgac ttttgtgaag ggtattcgca 2040
attcctttct cagcccatTT attttttttg agtagaggaa aactactgat ttgtttgagt 2100
taattttaca tccagccact ttgctgaagt tgtttaacag ctgtaggagt tctctggtgg 2160
aaattttagg gtcacttata tatactatca tatcatctgc aaatagtgat atttcgactt 2220
cctctttttc aatttgtatc ctatttgcac agaaggctaa tatccaattg aagatctcct 2280
tttgtgtctc aattgctcta gctaaatctt caagtactat attgaataga tagaaagagg 2340
acaaaaagaa gcaaacacac ctaagaggag tagacagcag gaaataatca aatttgggcc 2400
tgaaataaac caatttgaaa caagagaac tatacacata attaagaaaa ccaggagccg 2460
gttcttttag aaaatcaaca agatagataa atccttagcc agacttacca gagggcatag 2520
agagagaatc taaagtaaca aaacc 2545

```

<210> 44

<211> 2435

<212> DNA

<213> Mus musculus

<400> 44

```

tctctctgtc ctgcttgta ggaatcagca tgatcatgag ctgtggttag acatgatggt 60

```

WO 2005/005597

PCT/US2003/027106

ttacaaaatt ctattgaacc tggcatgaaa aaaaaaagtc tcgggaaata ttcttttttaa	120
gttttcagtt atttcagAAC ctactaaaa tatactgcta cttgctttta aagtcggttt	180
tgcgcacata cgtcttttgt tgccttcagg ttctcccatc ctctgtttgt agaaatggga	240
cagacaccat ctacaatgta agcacaaga attgccaaat gtcttaagtt catagatgtc	300
ttcatagaag tgatactatt atatttttct cttctctat ttcccgag tttttttttt	360
ctgaaaaagt tttttttttt aaagaagatt ggggtattga gaaaaatcct ttttgtctct	420
ttgccttgat gctgtctttt aaatgcttat tatcattatt aaaaggtttg tgtactttct	480
cagtgtttat ttttctctca ttgtttttgt ttgtgtttt cctcaagta catggtatag	540
tttcttgaa actagagggc gacagattct cagctcaca acggaaggcc aaaatatcca	600
ttgttagtca gccacagagg acaatcaagg tggcagagct gcctctagct gataaggtgg	660
aatccacaac tgatttgac tttctcagac aggtatggaa atcttcttc cttctgttt	720
gccttcagc aagctgttcc ctgggccaca aacacacttc attcacaata tggaccccaa	780
gttgggggac agtttacttg acacagatgt tgtactgtag atgaagacc aaggaaggaa	840
actgctatca gcttcgtga aatcaattct aatctgccac tcttgctac agggctctgc	900
gccctgttt ccaaagaatt gttctgtgga cttaaaggga ctcttcatt ttgaagaag	960
caccacaga ttgtatcaat gtgatgggat ctctggaaa gcctggagcc cccaaaccaa	1020
ggtgggacat tggctatagc taagcacctt taatgagcaa tatgccattt aatgagctta	1080
cagcgtgatt caatgtgtga ttctcaaat gcacatgtct ttcttatta tacctagaaa	1140
gccatgaggg aaacatggta cgaagtgact ttttaagatc caaagtataa agccaggtag	1200
tgggtgtacc tgctttgaat tcctgcagag acaggtagat ctctgagttt gaagtcagcc	1260
tgatctatag agtgagtttc aggacagcct gaactacaca gagtctgggg gaataacaa	1320
cagcaacaac aagatccaca atatagtatt agaccagtcg attttgttta gttatcagaa	1380
tgctagtggt ataacattga accatttctg actgaggtag tcctttcagt aagaagtcac	1440
ttatttctta agatgagaaa ttacagcgag ggcttctct gcttcgtga agtgagaagg	1500
ctcacaggct tgtactatga ggcagacttc agatgatcaa gtccattccg ggggtgaacac	1560
gcacaactgt cttgcaggg ctggaggaca gatcctgcc aggtggatgg ctcttcatt	1620
ctggctactg tcacatcttg gtcacaagac agaaaggcac ctggaccaca gctaccgcag	1680

WO 2005/005597

PCT/US2003/027106

```

cttcgacaga acagtaagga acccgacatc acacgtgcct gccgttttcc ttattttcac 1740
atggaaatgt aggcctgcac aagtcattga ataagtattg aacgtctact gtctgtccag 1800
ctttgtctaa ggagcctaaa gggagtttgt agtttggaat ggatttgtgg ctgactttga 1860
tactttctgc tgcctaagtc tttctgttta tggctatact ggtgtccacac tcttttctgt 1920
ttccttttat ttccacgttt taaagaaaaa gtctaacaac ttctctgagt tagcagcatg 1980
gtggcttctg atattttctc atctctcttt gttcccccct caaatgacag acatccatgc 2040
ctattgattt taaagtacct ggtaataaaa ggccctggca tccagcctct ggcagtcgac 2100
gaggcacgga tgcctataa gccaggcgag taggacaaa gctcactggg taacagtcaa 2160
taaaagatga cttgtgtgta gataatgaca aaaaatcca tctgtccag aaggagtgtg 2220
aaaaatcata tgtagcagtc cttgaccaac ctttttattt gataacctgg atattatcca 2280
aacaatgcaa ttacactaat atgcatgcat tctgtgtgaa attgagactt cagtaatttc 2340
tagttaatat tgatcatatc ctatacttta tcaaatttaa aagggttgtg ctcatcaaag 2400
gacaccatta agaaaatgaa aggtaaacca tatcc 2435

```

<210> 45

<211> 1718

<212> DNA

<213> Mus musculus

<400> 45

```

aagtgaccca cattactaaa gaatgtcttt caagagagga aaactaatg gccagtaaga 60
aaggatcttc acaaagactt tcogaggcat tgaggtccaa ttcttcaagg tcttcagagg 120
ctgccaaact caggctccca cctctcctt ccatgggagt ctgtctaggc tgaacttaa 180
gtccaaatga atgaatctgc ttgggggggt ggagcaagcc acagctgtga ctctagctca 240
ctgggggttt ctgttttata ggcggtcagg atcgagtctc tgaattatc aactgggac 300
taggaaaaa attgatacta tctgatttgt agaataggcc tgggtaggga aataactaatt 360
ttaaatatca ttcatcttct cttttatcca gtctctgcgc tgtaattgaa ttaggtgaaa 420
ggactgagtc caagctgtag tgagctcagg ggagcttgca caccgaactg acaaattaat 480
ctgtggacag cctcatccca gtacttattt agtcaatagt cagtgaatga gaaaagggga 540
aagcacattt ttcttttttc ttctctattt ccttcccttc ttcttccctc ctctctctct 600
tacttctctc ctctcttact tccttccctt ctctctctct tcttcccttc ctctctctct 660

```

WO 2005/005597

PCT/US2003/027106

```

cctccctccc cttttttctc ctctctctct ctctctctct ctctctctct cttttttct 720
ttcttttttt cttttttctt ttctttcttt cttttctatt tactcattag aattttttcc 780
aatcagcata ctgtgaacct tctgtatctt ttccaaaacc atcaatttcc agcttaattg 840
tttttccccc cttctgacta aaatgtgaac tcttgaagta aactatttta catgttaaac 900
ttcccagact gagttaagag aattagaaaa ggactcagga gataggaaat atgttcagct 960
ctgtggaaga gtcattatg gaaagtctcc caaacagctc tgcaatgaat gcattgtgag 1020
accacctata atcgatagac acatgtgtaa actgttaaag gaaatactta gcaaggtttc 1080
agaatttgag gctgatgggg ggaacttctg ctatttgaat ttataaggag caccagggtg 1140
cagggcacat cacactagca ctctgtgat cctagcacat gttattatat aagtctgttt 1200
gtgttagtgg ggttacatat gtgtgcattg gtgcacatgc agagggcaaa tgtgaacctg 1260
tgtgtaatto cttagggtag tgctacctc ggtttttttt aggcacaggc tctcattggc 1320
tcaggctccc cttatttggt tatgtttgct agccagttag ccaggggac ccacctgtct 1380
ccccagctct gggattccct ctacctgcca acaggttggg gatttttttg tgtgagttgt 1440
gaagatccaa ctcagggtt cgtgcttgct aacatagcaa gcatttatta gccatgttat 1500
catctctgct tctgggggtg tgtccattca ttaacttatt caataagcat tgtgaactgaa 1560
tggtgcaatg ttctactgag aagaacttag aaccaatttt ctgtgctoga atcctgactc 1620
taaaagatat catctgcttg aacttggcca aatcacttga cttctctgaa cccagtttc 1680
ttttttgtag aaggggtaat aataaataa ggggtagg 1718

```

<210> 46

<211> 3044

<212> DNA

<213> Mus musculus

<400> 46

```

tttttttatt ttatttattt attttttgac aatttctctt tgcctttatg ggggagagaa 60
agtttttctt tgcttaggag gaaaatgaca ggtctttact tggtgttttg tgctgagacc 120
acactcctaag atatatttga aaagtacctc agctgaagca gcctctgcta gttcacagaa 180
gaacacaaag aagctaccgc cacaaagctg gataagtcag taagagaaga ttccatggga 240
tctaagaaca gaaatctgtg ttttagtgto atcttattat cctacacctt tttcttggcc 300

```

WO 2005/005597

PCT/US2003/027106

tctctgtgct cttgaacttta attcagggta agtagccctt gatcccttc cctctctcag 360  
acacgggctt ccacattggc taccgcagc ctgcttctgg agactcctct gttgagtacc 420  
tgcccttgca gtggttgccc caaagctgta gtgagacagt gacatggttg cctgagactg 480  
tgctgtaagc agaacatgtg cggatgaagg ttctcttact ccagactgga ggagatgggt 540  
caaccatagt tcttcatata tggcgggatac tgtttatatt gcagacagca gtgacagaaa 600  
aattatgabc gatgcttatt ttatttcagt ggaagacaca attccatgaa tcagaagaca 660  
acaaatgcc aaaaaggacc aggttaaaaa ggttccaaga tcaaacccatc ttccaaaact 720  
caaccctgta ctccagagct gggcagactt ctattttttc catctttttc gtcattcagt 780  
gtcttcagtt taggaagcta atgttcaata cattctcag gggaggaaat agatagggga 840  
gagcggttc tctactctt tcaaaagtgt attcttctgc cctgcataaa agtcatgggt 900  
ctccagcaac cctaataatc cagtacatgt gcttagtatt ctacaatac cttagaaggg 960  
accgaaggt tgacatcctt ctggcactct cagtagagtg tttctgatat tctctgattg 1020  
cacttttatg ttgtatttgg tttctaaatt gaccattagt tagaactata tattgtttta 1080  
tatattatat ataatatctc cacctttttg ttatttttaa ttgcatcatg ctcagttcaa 1140  
ctttctaaaa tcaaggtttc aacatatcc cagatcacat gcatatgaaa gtttcaggaa 1200  
aatattatca ataacttcag ccattgcactg cattgttctt gcccccatcc ccccccccc 1260  
gccagtaacc ttgaggattt agggttatcc tatcacctca tgtttatttc ctacatctag 1320  
aaaaatggct gtgctaaact gtataattta taaaatttct agaaatttcag tcacaggggt 1380  
ctgccactgt gtatgtggca ttaaaatcat tttgtgacat ttactaatc acaaaaatgg 1440  
tctagttttt ggaccaaaact ttgcaggagt ttggaatact ggagactaga aggaataga 1500  
gggagaataa gaaattgttt ttaggcctta tgaactttat tgaattttat tcatgtttag 1560  
ggtgttttgt gactcgaatg ttttttctaa ttgtagtaga gatcaggaag attcatataa 1620  
cttaccatt taaatgagag aattatttg aatttaaaatt tcttgtgcat gtttagcaag 1680  
tgggttttta acctatatct gatgaaaaa gtcatttgggt tccttttata tgtaatgtgc 1740  
cttttacacc tgaggggttt atgtgtatgt atgtatgtgt gtatgtatgt atgtatgtat 1800  
gtatgtatgt attatgcata atatgtacat gtatgtgtag ataatagaac cataatgctg 1860  
cactcatgaa cttgcagtag ctatgggtgc ctgcacaaaa cctgctcaag atcaagctag 1920

WO 2005/005597

PCT/US2003/027106

ccaacattcc agctccagtg gcagagggac acatgggcoct caccctagtc tgagaagctg	1980
gtgacagcaa ggtctgctag gagagggaga gtcgcgtcctt ttaaggggtg ggtccctgg	2040
aggttcagaa tgatccagta gatggcccca cggctatgta tttatggaca gcaactaactg	2100
gcttcaatgg aatagatgtg tgtgtgaata aacatatata tggatgtata tgtgtgtatg	2160
tatacacacg tatttaaaga tatgctgttg ggaaggggtt atgggatcctt ggaattggtg	2220
tgtgtatgaa ataaatacat tgtatacatg tgtgaaatta tcgaagaata aaatattttta	2280
ataaaatgga atattgacat gatagggcctt taatgtacat attttctcctt tctttatttc	2340
tcttccaagt ttgtttctaa agactgattt ttctcctggc ttggggtctc ccattctgct	2400
tcatatatct atacagtttt tattggatgt tgagtatcaa taatatcata ttgcagattg	2460
caatattcct atgagcattt aaattgctta cagtctctatt taacgcctca gacttccatt	2520
ggagtgaagta aaactgccaa gagtgaagtt gttaagatat agctagcctg agggcccaag	2580
gaagttaccg tgaatgacac aaaggacaca tagctctgct tggcccagac ctggatgct	2640
ggagacctgt aggcactctg ctccaccatt ttgcaattta tgccttggtg tctgttaggg	2700
gctcgtggta tctgtgcag acttgggggtt ctgtttttgg acaggccttt gtgttcacca	2760
tcagcctcct ccaccagctt ctgtctctc taatgtggga aacggacctg ttaccatggt	2820
acttctctct ctgaagtctg tgatgtgtat aggggaggag ctaaggaggc aactggactt	2880
gctgcctctc caaggatccc ctcttcacc tgcaaacac tcttttatct atttttatct	2940
accttcttat ttagtcacag tgaatggcta aatttggctc tgccactcct gcaaggccag	3000
aactgaagaa cacattcact tgatattaaa actattttta aagc	3044

<210> 47

<211> 3100

<212> DNA

<213> Mus musculus

<400> 47

aagtttatag ctatactgtg tacatagtat atataatata tatgaaatat atatecata	60
gcaaaaagtc ctgcatgctt caattttctc atccctgaaa ctggaagctt cacttatoat	120
ttacaaacag gttccaacat tctctttttt gtgtctgggt ccagaactgg ttggaagct	180
gttaacatgg ctgttttgct tgcgtcacia ttgggtttcc atctgtgctt atttacagac	240
aaaattcaat gttgggagat gcttctcaag gttcaatctc agacctttta cttctgttgg	300

WO 2005/005597

PCT/US2003/027106

tttggttttg gtgcccgcga acggtgtcag gtgagcacgc tgagtccgct cttctccct	360
tggtgtttcc cctcgtctct gcggatactg tacagcaatg gtcaactttg ccacttgac	420
tgagttttga gtcaaaccta tttctttaa tgaagttgta acttcggtat aactcaagta	480
tattgtatat tctttgcttt tagttaaaaa aaaaaaagta aaacatttta gctaattaaa	540
aagcactcag gtgataatta tgtaggaaaa aaaaaaaaa acaatcttgc caaataatga	600
accatccta ggatgtgtag acaataatct gcttgaatat tttgtagct caactctcc	660
ccacgtttcc ccaagtaaa gtgaagtgc gatgattcag agctgacact ggatgctcaa	720
gtctccaca gggacagagc ggatggctcg aaggactgca gagcaaaaga gcggggagcct	780
gcggtggtgt gttagaacgc cacaggcact ggtgaggaga cagcaggsga ggaattctct	840
tcatttaagc atttctttct ggcctctgct tagacacgcg tcagaaatgc catgtggtag	900
ggcctgcttc tttgaagtc acagctaacc aaccccacc tttcctgcc aggctggcc	960
tcagctttca gtggcagccc cctagattaa ttgagctcac caagagtagg aaagagaatg	1020
gcagaatgga gcctgggac cacaaggact taggctaatt catttcttc ttcctttac	1080
ccttccaatg cctctgtac tcttgaggtt ttgttctgca cccccctcc cccaagtctc	1140
ttgtctgaaa gctgcttcat cgaggcatag gacagatacc gtaggagccc tctgccctct	1200
gcccagagcc tccaccctc acceccacct ttctccacc ccaggaata atctgcttcc	1260
cttctctaaa actgcttggt ttgcagatct gtgcagcagc ttcttggccc ccagggtatc	1320
ctggtgcaag ccattgttac aggaaggcat gcccagggg tcagctccct cctcccaaat	1380
ggtctctatc tatctgcttc ttttcagcag cctggagacc actccagctg tgcaaggtta	1440
tccagaaaag tctgatgttg gtagaggta gagggtaatg gggactagat gtaggttga	1500
ctttgtttct tctctgtgc cattgtttgg acaatattaa agctgcattg aaaggggaaa	1560
gtaattgatg actagtaggc aaaagtgaac ccctagtac acgttctagt agtactaact	1620
tctttctgta cctgtagtag tactaaaggt ttaagtatgt atgaatgcca gaagttgttg	1680
attcatgcag tagaatttaa ggggaaattt acttctttta aaataggctc attttttaa	1740
acctgcctct gggttttgag agagagagag agagagagag agagtgtgtg tgtgtgtgtg	1800
tgtgtgtgtg tgcagatttt gatacagcta tgttgagct gccatcgttg ttacaacggt	1860
ggtacttctt ggtctactct aacagttccc ttaccacagag gcattgtctcc atgaaaagca	1920

WO 2005/005597

PCT/US2003/027106

```

ggtaaagcta acgttttagct ccttgogaat catgggggtac tcacagttgc ctgttatggt 1980
acaggagta cagacagta tttttttttt taactctctt attgcctttt taagtacact 2040
cttctaaga aacagaaggc ttgtattctg ctcaggccat catcagtgcg gagaagcctc 2100
tctgcttggt ttatgttttc ccagcccgtg ctgcagctgg aggtcttgcc acattccaca 2160
gtttaccac tacgtttctg ttgccagtag ctcagaccac tggcagccac ttccagggct 2220
gggggacagg gcgtcaggta tcctcgtttc tctctgccct aactcagccc tcactcttct 2280
cgttttcttt tcctcttcca ccccatctgt gccatggaaa ctacattttt caaaggactc 2340
taaaaaactcc tatttctttg ttgttgtttt tttttttttt tagtttggtt ggtttttggg 2400
gtgttttggt ttggttttgt ctttgttttt tgagacaggg tttctctgta tagccctggc 2460
tgtcctggaa ctcactctgt agactaggct ggcctcgaa tcagaaatcc gcctgcctct 2520
gtctcccaag tgctgggatt aaaggcgtgc accaccaccg ccggccttct ttggtatttt 2580
taacaagtaa ttttattcag tatccaccag gaacagcaac tggcctttgtg tagttgtcga 2640
cggggcatgt ccgtgtcttt tactgttcca aaccattgct tatcaaaatt gttctcaggt 2700
tgattcaaaa ggagacctca ctggggacca gaatctaagt tctttaagtg gaattcagac 2760
gtccccagtc tgtccttccc tggaaacctc cagtcaacca cattccctct gtgaaaaaga 2820
aaggggaaga gaagagagga gagtgtgttt taaaggaaca tttagttgtg tgtttgaagg 2880
tcttttcttt caacaatata ggacactcct atccaaacct aggcctcccc ctcggagcag 2940
cctctgtcct cctgtgtctc tgaacagcct ccttcagggt gcccaggctg tgggcagggtg 3000
tgtcctttgc caggttggtt ttgtgtctct gcgttatctg gggggtgccct tgaataaagt 3060
acaacttcac gacttactga ttctggaact aagcagttcc 3100

```

<210> 48

<211> 2023

<212> DNA

<213> Mus musculus

<400> 48

```

gaggaggagg agccgacagg agagagatgg agcttctggc cagacttcgg aacaagaagg 60
acacaacaac cttgtaaggt cttgtagagg cgataactgg cagcctctgc cactggcgga 120
tagctgatat aagctagcag ataaggttag ggcaggagat tctttgccca ccgattgtgt 180

```



WO 2005/005597

PCT/US2003/027106

tctctggcca gttttaagat aataaaacag tctatgtttt tcttccttgg agaaaagctg	240
gacagagaaa gagggaaagcc acctgacagc ttggtgaagc taagcttcga ggggctagcg	300
ggaatgatca cgatgccgag gaaggcacta agccaggagc gctggcagag cctcggggaa	360
ggcaatagcg tgttttataa aattacacgc aacacaactt atatgcgaaa ataaaacaca	420
acgagctcat aagcagggtgc agggaggact gcagggtggc atgcctttct ccaaggtttt	480
tttttttgtt ttgttttgtt ttttttaaac tcatttagac acaacagttc aggctgacct	540
ctgttttgat ggtactctgag tgaaggctac agttggggaa caacaacaac aactactact	600
actacttact acttctacta cttctactac tactactact actactacta ctactactac	660
tagcagcagc aactactact acttactact tctactacta ctactagcag cagcaactac	720
tactacttac tactctact actactacta gcagcaacta ctactactta ctacttacta	780
ctactactac tactactagc agcagcagc gcagcagcag gctggctaga gagatggctc	840
agcggttaag agcacttagc tgctcttcca gaggttccga gttcaacctc ctggtgggt	900
cacaaccatc tgtaaatgcca tctgatgcc tcttctgggt tgtctgaaga gagcaacaat	960
gtactcatat acattaaata aataaatctt ttaataataa taataagcct cagaatatat	1020
gaccaacttg atcttgcct gagccaaact atttttctat gtctatagtc aagctgtttt	1080
tatgtcagca atatgggatg gctggcaggc atgaacaaa ggggttacag ctaagctaac	1140
ggtttcatca atgatcatgt gccctagagc ctgggattta cctttgagaa ttocgtagata	1200
gaaacgatgg gtttgactg ggtcttctcc taccatctg ttagtatgg ttaaatgtcg	1260
ggtttcttta acgttgggtg aacaggctcag aagcggcatg catagaaaca aagctccaag	1320
ctgctgtctg aagcatcatt cagagttcct ttacccttta aggaccttca ctcagataag	1380
actggtcccc tgctttaact caaaagaatc tcggagttag ccaatagtga accagagccg	1440
gctcttgtgc ttgtttccct ttgtttttta agatttcatt ttggtattgg agaataacct	1500
gaacagttaa gagcacaaca gaaaaccag gtcagttctc agcacctca tccagtggct	1560
cacaagtgtg tgtaactcca gctctgacc tgggagaatt gagaacgctt gctcctctgt	1620
gtggtcgaca agctccaca tgggtggatg gtctgcacc atctttccac atgtttacaa	1680
tttttttatt tttttatttt tggtttttcc agacagggtt tctctcgcta gccctgattg	1740
tcttggaaact cactctgtaa accaggctgg cctcgaactc agaaatccgc ctgcctctac	1800

WO 2005/005597

PCT/US2003/027106

ctcccaagtg ctgggattaa aggcacgccc caccactgcc cggcatgggtt acaatttttt 1860  
 attttgcgt tatagtctct ttccatttg gtaaaatcta gtcattttac cttgggacaa 1920  
 aacctcccc tccccccacc ctgtttttaa aattttatct attttgtttc ttgttttaga 1980  
 gtggggcttc atgtagtcca ggtttacctt atgctatgta gcc 2023

<210> 49  
 <211> 3693  
 <212> DNA  
 <213> Mus musculus

<400> 49  
 gctttctgga cttagggctc agtgaggaaa gcacccaaca totatgacaa atagtgaata 60  
 agaaactgta cattaactat ggagaaagag ctgtgaggga aaggaggcct ttgacatttt 120  
 agactatctc ttacccttc tctgcctct taattaagag gtgctttctc ttgcaactgg 180  
 accctggaaa tgatacagtc atcccgctt ggttctctct ggcgggaac ttctgtctgg 240  
 tcttcccttc ctgcttctag aaaggaaaca agaagtcatt taaagatatt gctgagatca 300  
 gggacgagtc atttcttgtc tcttttctgt ccttctgaag gtcactatga ccagctccac 360  
 ctcagacctt agaagttacc cggctctgag agaggagaca aagtcgtcta tcaactcgtg 420  
 gcttggaagt catgaatctt cctgccagcg agctatttct ttgcagacac ttactatgto 480  
 cccagttctg ggttagtggt ggctctgggc aggaccaatt agggatgcag gacaggaaac 540  
 ataaagcaag cttccaggaa atgaggctcc aagttcacag tcagctttat ttaagggctt 600  
 gtttgcaagc acagggagag ggcgtgcca ggcaagttaa acattgtccc tggccccaag 660  
 gggatggatc atggcgagtg cagacatggc ctggtgcaga gagggtgaga agacagcctg 720  
 accactgata aggtaagcct atagacagtt gtcacaagca tgacactgct cactgttgct 780  
 ctctaactct ggctcagaat caccggcatt ccattagtgg caactgggct acgtctgggt 840  
 catcgcaagc tgtcatgtaa ggagaatgta tgtcaggagc cactgtgccc tgccccccac 900  
 cccccccgcc ccactctcag gtctttccca gggcctacct catagtcttc aaacctttca 960  
 agactgggtt aatgcctctc ctaccggtac attttaagcc ccgctacttt gtttgttact 1020  
 ataaagctgc catcagacat tccagacccc caaggagcca gacaaagccc aactgtcttc 1080  
 ctgtggctct gctagacaca tctagaataa ccagtcagtc caatggacag gggagacatc 1140  
 tctgtgtagc ctggcaggtg ggggaagtat ccgtgtggg acatacctgc ctgtctcag 1200

WO 2005/05597

PCT/US2003/027106

ttatctgaaa	ttocagtgtg	ggcggacatc	ctgtactttc	tcagcagctt	ctgtgaaatg	1260
ggtgaatcca	gaaaggacaa	agactctaga	ggattctgaa	ggccccagc	aagggtcaga	1320
agggacccta	ttactgtggc	tgctaactgc	ctgctgtcat	gtctgctggt	atacccagcc	1380
ctaggcatag	ctcctctgtg	cactgggatg	ggtgtgccgg	gccttttcct	cctctccacc	1440
actaagctct	ccccagggat	gggacacagt	gagggtccca	tcccaacctt	ggcccaggac	1500
tcaagaggcc	caccaggcca	tcagaaggcc	gttcttgttt	cctcactgac	tagcagcaaa	1560
atgcaacct	cttggctcaa	acaatacaga	aaatgtcccc	tccatcttaa	ttagtcttag	1620
cacaggcagc	tccagtgttg	gctaattcag	tgtttagcga	gactgttatt	ttgacctgta	1680
gcctgtgcga	ctctttcttg	taccagggc	atgtgcctt	atgtccttta	ttggcttcag	1740
atggctgctg	cacgtctcaa	tgtctgcctg	aggacatggt	aacaagccat	caaggagaa	1800
gagagggtgg	cttgcccaga	tgttcaagcc	catgatgtca	ttctcaggaa	ctcccatcag	1860
atagctcctg	tgtgtgtggt	tgagctgaag	ttgtcacgtg	cttgcatgta	cgtcagccta	1920
aggcacagca	gtggcctctg	actgtcactg	tttgttctgt	gagtgggtccc	tggtgtgtca	1980
gtgcatggag	tgagagacaca	cacacacaca	cacatacaca	cacacctgag	ctacaccagg	2040
ttctctaacc	actccctacc	ttattctata	aagacttoga	ggttgttgtt	tttaactctg	2100
tttctcatta	aaaactcaag	cattacagag	aacctgact	aaaaaaaaatt	ccaataattt	2160
aactcattct	aaccatactt	gggtctatga	caaattacct	aatttttattt	catacaaatg	2220
taatcogatt	ttaatttagg	ttttgtttt	tctgtttctt	tctcttttcc	ttattttggg	2280
cttttgagat	gagagtttta	agatgtatcc	ctgcctgccc	tggaactcac	tatatagacc	2340
aggctggact	caaacttggt	gccaccatct	gagtattggg	atttcaggcc	tgccaccacca	2400
ggggcagcta	acctctact	tcatcatttt	aatgccactt	cacacgtttc	cctttgccat	2460
tttaatttaa	ttatactagc	aatcacatgc	ggctttggtc	aggttcttag	gtgcagaccg	2520
cagctctgtc	tccatggagc	agccttatag	aagaacctcg	cggttaacca	tttcacaggga	2580
gaggctacac	attcctcatg	cttaacaaca	tccagtgagc	aatggctggg	ggaccacaaa	2640
ctgatgtgtg	catgggcatg	tgcatgtgtg	catgtgtgtg	tgctcgtgag	cacacaggct	2700
tgcatgcatg	tgcatgtatt	gtgcatgtgt	gcacatgaag	tagggcatgg	catgccttag	2760
tgtgcatgtg	gaggtcagaa	cggaggacag	acttggggag	ccagttctca	ccttctacct	2820

WO 2005/005597

PCT/US2003/027106

tgcttggcat ggggtctttg gccatttctg ttgctaagct ctgtacccca ggctggtga	2880
cttgtgagct tctgggtgat tctcttgtec acaactccca tcttgctgta gaagtgtgg	2940
gattgcagat gcaggtgtt gcagctgggc tttttctgtg agttctggg aatctcaggc	3000
tgccgtgctt atttgtaaaa tgctttaccc gctgagccac ctccctgtt cgtgtctcag	3060
ctggacagc tgacatcatc cttcttttc tatgtagc tgccaccac catggtggca	3120
gaggtgcaca tatatatata catatacata tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg	3180
tgtgtgtgtg tgtgtaggaa catattcata aaatgtatcc gttttctct cactttatta	3240
catcattggg tgatattccc ctgaagataa catggtgtgt cagttacggt ttctatggct	3300
gcaagaatac accaagacca aaaagcaagt tggagaagaa aggggttctt tggcttacac	3360
ttccatgtca ttgtcatcac cacaggaagt caggacagga actcaagaaa cacaggaacc	3420
tggagacagg agcagatgca gaggccatgg aggggtgctg cctactggct tactccccct	3480
ggcttgctca gcctcctttc ttacagaacc cgagaccacc atgctttctt acagaaccgc	3540
agaccaccag tgcagggatg gcaccacca caaggggctg tgccctctcc tgttgatgc	3600
taattgagaa aatgctttat agctggatat catagaggta ttctctctgg agctccttcc	3660
actctgatag ctgtagattg tgtcaggttg acc	3693

<210> 50

<211> 4226

<212> DNA

<213> Mus musculus

<400> 50

tagtttgatc cacatgtaag acgagaaatg gacaggggag tataggatgg ggaggaataa	60
aaaggaatt aatagaagat tggttggctg agagtgaaga gggagcttc aaaaagtga	120
ctagagtcaa ccaaccaact aaccaacca acaacaaaa aactcttgag aaaatagcaa	180
gttactgtca ttattagagt agacgtctc tctctccctc tatctcttc aaacacacac	240
acacacacac acacacacag agagagagag agagagagag agactagagt gagagagaga	300
gagagagaga gagagagatc tatatacccc cagtgcgtct ctcaaaactg ttctcaagga	360
aacaggtagg tgacatttct aattatccct tccatgtcct ttogaagcat catcttccat	420
tcataccttt tgtagctaat gactctaact aatgggggct ggaatctctg ataagccaac	480

WO 2005/05597

PCT/US2003/027106

cctatgaaaa ggattcacta gagagaattt agttgtgctt ccctataggc tcaaatgtga	540
tccccaatta tggattgcta cttctcaata accttcagga gcttcacact atagttagtt	600
ttagggcttt cagatttaag tcacaagagg tacacacggt cttttcagtg ttatccagggt	660
gataatgcaa aggaagaggg gcaagcaatt aagtaggaat ttagagagtc agagggagag	720
tttcaccacc agtgccctctc ttcagaatcc tacattccta gtcatagagc atccctttgt	780
ttttcttaat ttccatacaa atatcagtaa gctattttac cttgtctctgc ccttggtcta	840
caggctttag gaatctcagg tcaactggag gttattttct gaatgaacct tcagatttca	900
ctctggggac caactccctt cctgttgaca cagctaagta cactgaacaa caaaattgaa	960
atgtgtctta gactccatgy aaccagcgag gttaaatctt tgccaaggtt ctagtgcctc	1020
ttggtgtact tctggagatt ggagcccaa gcaaagtttt cttggaggac agaatacaag	1080
aagataaagg aactaaagtc aaaacagcct ggaaatgaga atgagagatt tccagcagg	1140
cactgtctgt aagagccttg atatcattgc attaaagctt cttttccctg tagacaatct	1200
ctccaccatc atttattgag ggtcaatgct tgtctcttat gtcttcagga gcttagcaga	1260
gtctctgtct caatgtatat tcttggtctc tctgtctctc tgtctctgtc tctctgtctc	1320
tctgtctctc tgtctctctg tctctctctc tctctctctc tctctctctc tctctctctc	1380
tgtgtattaa tcaattgtta ggtgtttcca actgtacttt aattccaatg gttgctaata	1440
aataatgttt cttttatttt tcatatgtga ctaacatacc agtttttctt tctttttaag	1500
ctaaaagtgc catggaattc caccaacaaa aggggcttaa gaatttgaaa acaccatttt	1560
tcagatatag cttaacagca tattaatatc atatgtataa gctgcttaac ctctctgtgc	1620
ctcactttca tataaattag aattataaat actactctt aggatgaaga aaaaagggaa	1680
tggggatgcc ccacttcttc tttttcactc cccctaacac ccaatatgca tgaatgtgac	1740
ctctcagagt tacttatgaa ctctgctatg tatggagcta aggcctgtgc tatgacctct	1800
cggaaacagca ggtaaagta gggctcatgt gctcccaatg agtccacatg gtatgcagct	1860
gctttgtctg tctctggcag tcagtatcca tcacaggggt acagttaac agcgtctcag	1920
acaggatatc tgtggcttac atgaagaagt ggctcggtcg ctaagaatgt attaattgtt	1980
ctctctgtgg tcagaactgg gagcgtggca gttcattgaa aggggtacaa tctttgttca	2040
agtagaacat gagaagagag agaaagagag agaggggagag agagagaggg agagagaggg	2100

WO 2005/005597

PCT/US2003/027106

```

gtgagagaaa gagagagtaa gagattaatt acttcttgac agaatcaaga aggataggaa 2160
gagcttgccct tagaatgtga atgtaattag gaagataaag gatgaaagaa taactgggaa 2220
gggggcaaca ttactagaat atctttttaca gacaggaggg tgaagcatca tgggtatactc 2280
tgatgagcct ttgggcatgaa cgaagctgag atagcagggg cagagaatgc agtgactaag 2340
aaaggacttg tccatccttg gagcttaaat gttattttcg gtgcacgata aacttgagaa 2400
ttgatggcat cacctgaaga cggatctgga ctcttagaaa tagctcccac ccactttctt 2460
gagaccatcc tacacctatg acaagatcta tgtcatggtg aattacagct ttttctttgt 2520
gtcaacccaa ctaggttata catgaatttt cagtgtcctt gtcccaattt cctgaatcac 2580
aaaagagcac aggaagaatg cccctcccca tgccaaccga atccccctgt ctatggatca 2640
gcacagcatg tcttaaaagc tgagtgcgtc taaagagtaa ttgctattgt ttaactttac 2700
caaggctaata ctatcacacc tcaccacagag aacctctgat ccactctttg agcattctct 2760
gtcctgaggt aaaacataac aagcaataa ataagaaggg aactgtgtgg aaacctctt 2820
tgtcactact gaagcatggt catttattta gcaaaatgtc cataattttt aaattgcttg 2880
aatcagccac tggctatttg gtatcttcaa ggggtcccca tcaggaataa tacttcccca 2940
ttacctgcaa aaaaaaatat tgaggcaggc ttttgatcac aggaattaat tacatgcaca 3000
gaatttcatt gctgggagca gcaagcagct ggttctcgca gggccctggg tgaactctct 3060
tgccaaotcc ccttctatgc ttgatctccc ctgcacacct acacccttgc tttctttcat 3120
tatgtctcac aggttctatt caatggggga aaattgtaat taaaacattt acaagcttt 3180
ccttatgacc gcccttaagg ctgcgaacct tcacaattca atcttttttt ttttttccaa 3240
ataaggcaca atgacagagt ttccaggaat ttcttctcgc gggactcagg cctcctagaa 3300
tgatattaat acattaaaaa aaaaaaaaaa acttcacaat gaagctctgg gataaaagga 3360
gagcacgtat cttottcaag ggaggggaga atattgtaat gatgactaat tattctcagg 3420
agccaacagc ttccctggtt gtcagtggga tcagttaaca atggcttagc ttgtctatct 3480
tcctattttt cctgttaatt attcctacct ctgctaccaa gagaaggggc ttgttttctc 3540
cttagatgta attagagtaa tgaaagggtt tataatattt atatatttta tttctaggac 3600
tctatttcoat tttactttca tgaggacag aatatagaat gcaaaacaga aacctcaagt 3660
tctagggttt tgtgaagtct tacagagaaa attggtttca ccataatagc aattaggagg 3720

```

WO 2005/005597

PCT/US2003/027106

```

gataattcct agatgaacaa cctgaaatta ctcccttaaa ggcaatactt tatataggat 3780
tttgagaagag gtggggaaga tgaggtgaca attttggtgc attttatttg tgttgatcct 3840
tgtattttgt gataaagaag gaaggcaaac cattggtgta ttctctata gacctgcatt 3900
tgcatatggt ttgtctctgt tgaatagatt ttggtttgga tgacaaatta aatccccagc 3960
ttccaaacac ccaagttctt ttgttcagaa ttataagcc aggatgccca aatacagctc 4020
ttcttcaagag gtaaaaggggt taagcaacaa gttgctagac aattattctc cttttatatac 4080
taacaaaacc acctctctagc agctcagaac acatagcaaa tagcatttaa aaggtattat 4140
gccccatcat cacaggcatt tccatggcaa tgaagtgatg tggcacacac aaacaaggat 4200
gtaccagttt ttttttcaac atgctg 4226

```

<210> 51

<211> 1560

<212> DNA

<213> Mus musculus

<400> 51

```

gcctacactt ctgcactatc tgtgatcagg acgacagtc aaattcaact atatattaac 60
ttcaattact tgagggtgtt aaaagataaa agtgactca aggttttcag catctgaaaa 120
tatatagaga aaaaaattat agcaactaa tacttcatgt ggaagtatta aatttaaaat 180
ttaaattatg taccacaca ccacagttat atctttaaca gtactaacac cagatatgca 240
gcctaaagta cttctcacag acttgaactc catctacaac taacattaag aaataaaaac 300
aaaaaccatc ttcataaac actgatcata aatttctatt ttttgtctc taacttgata 360
ctatatattaa ttaactgact cttttgttt aggtatgctt acacctaaaa gatggagatt 420
gttttgatac taagataaaa ctttgagaat ctttaccaaa ttttaccatt aaaaccctta 480
gtataaaaga ttctatgat caaagtctaa tagttctttt taagttgtat ttttaaaata 540
ttaatgatta gatgtccac ctgctgaaga agaatatgac ctggaattcc aaattgaca 600
catggttcat aaacgaaagt tacttagaga aaatagctg aaaaatgaaa aagaacagcg 660
aatccttggt ctaagggaaa gagaaaacct gcatgtgtaa ataagttcca gtggaagggt 720
tagaatctgt cctgtgcccc atgctgttta ttaattactg cagtttaaaa caacaacaat 780
aacaacaagg aggatgtgtg aactgcattg ctcttcatt caggtcagct tggctttctt 840
cttgccaggg cccttatgcc ctttggcctt tcttctcaga ttgcgcctgt ctactacagg 900

```

WO 2005/005597

PCT/US2003/027106

```

aacttcact tcaatctcct ctgagctgct atccacagct ttctctgtg actgtgtaaa 960
ctgttccagg tgctcagagg acgcttcaga ctgttctct gactggctct tctgtcctgc 1020
attctgtgga aatggcgcgt cttcaagttc tacctctatc agagaactct gagtatgccga 1080
tggttctctg gccctcaggtg ctccctctct accctggctt tccactgagg aagtagtggt 1140
gggtgataaa ttctgagaga ctggttcttc gggaaattct ggtaccacag aatgggaaa 1200
attaccatca gacttttcta tatttgatac agtggcaaca ttgtctgagc tccccaaaag 1260
tgttttcttt ttgaaaactg gggacagatt ttcttcagta tgtcctttat catcagatgg 1320
gctttgatog atcaacattt ctgagtcagt atcaggtgag gtctgggaaa agcacacaag 1380
aaacaggta gtgaggcatt ttacaatgca gttctaagc gattcattct caatgtcact 1440
gtgaagacct ctggactcct catttttggt cagcatgaag acattatatt aaatgcaact 1500
caattttctc aaaattgtct catgttgact gtaatacaat aaaagaaatc tttatgcccg 1560

```

<210> 52

<211> 2849

<212> DNA

<213> Mus musculus

<400> 52

```

gccagcctca cgggcctgct gccactgtct gccctgtcct attgcactgc atctccgaac 60
ctgagccaaa gaaataacta agaatttggt catagcaatg agaaaagtag taactaatc 120
aataacctgt gcttgaactg tttcttttac ttgcaccaa tgcatttatt cttatataaa 180
gtcttatata aaatctcgtg tgtctctctc ctctctctct ctctctctct ctctctctct 240
ctctctctct ctctctctct ctctctctct ggttttgctt catccattca tttgtcctag 300
agttcctaag ggaatataga tctttccctc tccagatctg tcatagcact ttcttcacat 360
ctgtactctg tgtcttctgt gtgcctgtgt gtgcacaaag gccacgcaa taagaacacc 420
catctccctt gccctgcgtt ctgtttggag ggagaacttt ccagtgcacc cagtactgt 480
gtcatctctc ttcacactt cctttctctg atttccatg gtagagaac acaaaattag 540
ccttcatcgg tattttaagg gaaaacatgt aaaagactca caaatagatg aaaatactct 600
cgtaaatc atggaagat tgaacatcat atgatctggt tctatgcagc cttttcttgt 660
ccttgagtta ttttacattg ctgtaaatca cattctacta gtaacaatgc aaatgactca 720

```



WO 2005/05597

PCT/US2003/027106

tccatacaaa	tgcaaatatt	acctaatttg	agattcgact	gattattgca	tgtgcctttt	780
catgtgagca	tgtgcatggt	gaggccatgg	gacagtcctct	agtcttacag	ctcagtagct	840
gtctgtctta	tttcttgaga	cagtgtctct	ttctggcttg	gaactcagca	agtagggcta	900
aactggtagc	caaataatcc	cagagatcag	cctaactccg	cctctccagg	gcttgggacta	960
aaatgtgttt	cacagtgggt	ggtattttaa	gaatgatctc	taatgtgggt	tctgggaatt	1020
taccctatag	tcacacattt	actattggcc	cttggattac	cacagtttct	ttctttctac	1080
ccaatgctcc	cccttttgcc	tcttgcttct	actaccagta	tggggaacac	aaatatctg	1140
tgtgcctccc	aaactgtcta	tgtgtctggg	ggcataaaat	tgtttggaca	atgtgggaat	1200
aaagtagaca	acaacaacaa	caaaaaaaag	gaataaaagt	ggacaggttg	aagacaaagt	1260
ttacaaggaa	acctgacaaa	gttggcctat	gggttgcttt	tggatcaaga	atcatgagaa	1320
tcattgataac	ttctgtgtct	ggcgtgaaag	actgggtctc	caggggaacat	ggatgtagga	1380
agaagtgttg	tgtgatgagc	cgggggaaaa	gtccttaaaa	tattgttttt	aaaaataatt	1440
gattacatac	aggcatatag	aaagttaaaa	gcgaacatcc	ccaggacatg	gtaaagattc	1500
acgtataaaa	ttctgcctca	agttaccacc	cttttcccac	ccaggacaga	agttcacaaa	1560
ggacatccac	tctgttccca	gcttgacgcc	attctttgag	gcacaattgc	agtttttccc	1620
actagtgagt	ctgtgttctt	ttgtttatga	actggaagaa	aagacatgcc	ctgaatctcc	1680
ctcatagact	aagaaaaatg	ctttctatgg	agtatttggg	ttccaatggc	tggaaaattta	1740
caggtcactg	cttcttaaaa	ggcacactgt	cccttgagaa	aggtgaatat	gactatcccc	1800
ccattgtctc	tatggtagaa	aacatgtaac	cattgattgg	gtcagagtgt	ggcaactgaa	1860
atctgaaaaa	ggaaatttta	aatgactatc	ctgacttcac	agcctcttgg	ccaaattggca	1920
gtagcattat	cattgagcag	gttaaggatg	ggcaatgggt	gttaattgag	ttatagtcct	1980
tgtagatgaa	atgtccaaag	tgccgcaggc	ctcaggaaaag	tctaagtctg	ttagatgcat	2040
cctgtataat	agaatacctg	caaatgtctg	taaacaaatt	aggattgctt	tttgagtggg	2100
aatgtatagc	tctgcaggga	catgcgaaat	gtatctggta	atgtctgtaa	agcacttgaa	2160
atgttttttt	ttcttttagc	cacttttctc	cagggatact	ttgtctcccg	tactttcta	2220
tccaatgata	aagaataatt	gtcaatttcta	cacttagtgg	gttggtgcaga	gtgactcacg	2280
aagctattta	caacacatcc	agaactcacg	attacatttc	tcattcatgaa	gatctgcctt	2340

WO 2005/005597

PCT/US2003/027106

```

tctaacttgt gacatttaga taccactttc agcttgcagg agtggcagct ataacttcgt 2400
ggctccttagg gaaaaacttt actaccggag tagaagaatg tagtaaaaag gagcgtaggt 2460
ttggaaagaa catttggtac ctgacacctg gctctcacat ttatgagcta cacaatctgg 2520
caaatcactt tacctcctgg actccagctc tcttacctgt aaaatgaaga caatggcacc 2580
tgccactcaa ggctgtttgt gtgtctcggt gagtaatgta tagttcttga cagtttaatg 2640
atgccaatg aaacctcctt tttccttcta aattcattgc aattagtcaa ctcaagagca 2700
attattctta aatcttccct ctgtctatgc aggtcaatc agaggttaac tgatataatt 2760
ttttttaaaa tagccaagtc caacatacat acatgcactt agattgttaa atagttcttg 2820
actgaacctt aaaaaacaa aacaaaatg 2849

```

&lt;210&gt; 53

&lt;211&gt; 3551

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 53

```

tattcactga agaacaatt gactttcgct tctctgttgt caaagtgccc cctgggtgata 60
gtgctgcagt ggctagatag agcgagcaga atggcttcct cctggctggt gggctggcag 120
cttcaactggc actgccaaat gtacttccta ttgttgtgc aagggaattg gaacagcgag 180
gcatttatca tatcatcccc tactcctcaa tgcgagcaaa aaaggagaag ttgtcaatga 240
aagaaaaga actgtaatcg cacatttaca tatgcttcta attgttgatt tggggatttt 300
ctatgaatat agctttacaa aacagatgct gtttaagaaa agggggaaca taattttgtg 360
ggcaatgaat taagtgtttt tgtggccctc tcatcgtag ctaggagcag tttgtggacc 420
gcgtctgtga acgoggtcca taattgtttt tcacacataa gttatgcaa tgagctttta 480
tggcaactgg cataacaatt agcatcctcc agcaatat tttagcaggta attgcaaaat 540
ttctaaattg tacatctgac ttgttaatta ggcattgacag aggtggttaa atagtatatc 600
tcaggcagtg gcagccagga gctgcttgaa atgcaaagag caaggattga ttggatttga 660
gggctgcaat tgtgggagca gggctgctgt caagtgcgc cttagcagctc tgcctccagcc 720
gctgcctcag agcaagacca ggacttgctg caaggatcct gccacttaca agcctgcttt 780
atttaactca acaacagtc cttcccccac tatctgaact gtttatgttg tacagtttgc 840
tggccatcgg gatcattgaa atgaggtagc aacacaaaag aagtctcttt gggcttgagt 900

```

WO 2005/005597

PCT/US2003/027106

tttaggaccc	tggaagtta	ctttctattt	taaagtctgt	gtcagcactt	gccacttaaa	960
aaaaaaaaaa	tgtttagata	ggtaaacaca	attccaatt	tttattgaat	gtaaatTTTA	1020
gttatccagg	catcaagtgt	gatcattttc	tttgtataa	tttaactttt	caacatcatt	1080
tcctttcatg	attggcatgc	ttggggaata	ctattttgtt	atttatttat	ttttaacaaa	1140
gtaagagaga	aagagagtga	atgtcagaac	tacgtaaagt	acattggttt	actttgggaa	1200
atctataaaa	tgataatatt	gaacatagca	tattattctt	agattttata	ttagtaaaga	1260
attctctgtg	agtatgggtt	aagtaatttt	taaagtactt	aaaaaatttc	tatggaoggt	1320
ttcatagtct	gaatgggata	atttgctaag	cataaacatt	agtgaataga	gcotgatgac	1380
acgtgtgtat	ctgcttgtgt	cacgatgaac	catgctcttt	gtatttaaat	tagctaatta	1440
cattttttctg	tgcatatagt	acacacaagt	acaccacata	tgaagtgaag	catgtatgaa	1500
gtctgatgtc	atctttgaat	tcacatatat	tttcttgact	aatccagatt	atgtttaatg	1560
ttgaaatggt	atattttcat	ttaaaaagta	aatgtttctg	atgtgcagct	gtgctaatat	1620
tttacatttt	cttgtagacat	gtgtatatgg	agaaagtgcc	atztatgata	tgttgtctac	1680
aataattttg	tcattgagaa	taaaaggctt	aaattcatcc	accagtgga	acattttgtc	1740
atatattatt	taagagatga	aattagtga	cagttgggct	ctttatatgt	aggagatgtg	1800
aaaatagcag	aacatttacc	atgaatggag	tgcaacatta	gcattctcagt	gccactaaat	1860
tatacagtag	tagtggtagt	gtattctata	gacatcta	aatagttttc	ttgttttccc	1920
actttcttta	tatgtgtctt	ttatatggcc	tagtttcata	ataaagggtga	tattaattat	1980
tggttaacct	ttttagagtgt	atctatcaca	tttgaaacta	ttgtattttog	aatgagaata	2040
aaacgttgtt	ccaaatcatt	acattttactg	attaaatgct	caccgatttt	tatccattgg	2100
tgtattttggc	aatttaagta	agagtttacc	acagtaatgc	ttcagtggtat	aatattttgga	2160
atagagtaac	catttttaatg	agttoatoga	gggagattca	gcaggggagca	tttcaggtgt	2220
attacggctt	ttgtcttgtc	aggatgcaca	atctccatac	cattagagaa	aaggcttcag	2280
agtcccactc	atctccgcta	ataatgatac	taacaacaac	aacaacagca	acaacagcag	2340
cagcagcagc	agcagcagca	gcagcagcag	cagcagcaaa	gacaaaaata	taacttagag	2400
cttctccttt	ccagtaaaagt	ctgggcagca	agatagaaaag	cacaggcagg	tcgagtgttt	2460
ttaggaaact	tgtaaagcga	ataccatttc	tgtgggttaa	atttccatca	catttttaac	2520

WO 2005/005597

PCT/US2003/027106

tgctctaata ttgatccccc tacagaggaa tgagactgaa gcctggtagt tattagtata	2580
aagagggtca gctgctgaga cggccagag cagaggctct catggtaatg atgctgctat	2640
ttatagatcc ccatctcatt agttgcagag ttccaaggaa gagattttct ctatggggaaa	2700
tggactactg aagttcattt tcttcctcac attaaggcag gaacgtgaac aaccttcagt	2760
ataggatgtg cgattatggt atttttgag gggcagttta ttcctacat gtatttgcca	2820
cagtaaatgt acatttaaaa cataatgtag ggactcagaa atgccagctg ctgttttggc	2880
cgaatagtac attatgtacg ttgctcttga tatccttgc attttttttt ctgttaaaaa	2940
ttaaatttca aaattgtcc aaagctgagt ataatcatgg tcttctcttt ctccgagtg	3000
ctttagagcc taagaaggat tgtgagaagt gccagtcgcc ccaggtccag tctgtctaca	3060
gtgtgttatc tgtctatatt tgtgatata gtaattgtgc ttctttctg gaattcttga	3120
catttgagtt atttttttcc cttaagaga atatttactt agctagtatt cacttaatta	3180
gaactgactg tttaattgtt tctgggcggg tatttatggt attttcttgg ctatatttgc	3240
attccagaaa ttaagtcccc ctgccattat tcggcaagcc ttccatacat tagaatgatg	3300
aattgaaagc agaaatggga aaaagactgc aatgcaatga aaatttaac agcgtcttct	3360
gctgctttaa taaggcaaat aattcttatt ggcgcgtgtg ttaaggtttc taattattaa	3420
ttcataacaa accttgcat attctgagtg tgcacgaca gctccacttt gctgcttgcc	3480
aacaggcaac cataaaaact taaaagcaga tgtaaatgtc taaaacaagg agaatgatta	3540
gatctaaagc g	3551

<210> 54  
 <211> 2244  
 <212> DNA  
 <213> Mus musculus

<400> 54	
gcaatggagg tgggtgtcag acaagagag tgggtttcat gttcaaggaa gacattctat	60
aagaagtgat ctgagaccat gggctagaga agtggacaga gaattgaacc aggtagctct	120
tcagagcgag gctaagagct tttagagtcac ccetagcaca gggaatctgc tgagagagtc	180
actagatata tgcagcctgt tctaaggtca agattcttgt caactcttct tctgaggtgt	240
ttgtgtttag aagctctgct tctagaagct cggttcctag agcagagatg gtcataaggtg	300

WU 2005/005597

PCT/US2003/027106

gcgaactcca aagagggtgat ggctagaagg gacaaagggt ggtctcatga gactaaagtc	360
ctagttttga tgtgatctac ctcttttatg tatgtgcttt ccaactgtaat tccatgcact	420
agagctaaac tgatgatgaa accatgcttt tgaacatcta gaaatgtgat ccaaagaaac	480
tagagggaca gactgtgttc caatgggtcag atgcaactct ctactaact gataggaggc	540
actgttcttg ttatgttggg ttatgtttta ctgtaagtaa tgttcctcta gcaaacgcta	600
aactactttt aattttaata agtcaaagat caggcaattt aatatgtata tagaatttgt	660
aaattaattg tataaaataa ttacatata cattttataa cattatagca catacattta	720
tataaacaat atagggtaag catttaagct tatttgttga ggtatccaag cctcaacaaa	780
gtgtggggta agaaacacca atagagatgg ctccagcactt tgtcctgtgc ctctctctgt	840
ggctcactct tgtctctctg cacacactct ctctctgaag atggcagccc aagttcacag	900
ggcgcatgga gccctgtgct tgctatagag ccaagaatga ccatgaagtc ctgacctcc	960
tgctctaac ttccaggatt ataggtaac accacaacgt ctggcttctg aagttctgga	1020
aatcaaatcc agggctctgt gcatgctagg caagcactct ggcaataag ctctgtctct	1080
ctctgaagag agactctctt ttttcttcca gtacatttgt aattgaaaat agacaccact	1140
ctcctaactt cctctctcca accccttcta tgcaacccca ttctccagcc agttggtagc	1200
ctcttttcat tactattatt ttctatctat ctatctatct atctatctat ctatctatct	1260
atctatctaa tctacatata atctatctat tatctatcta atatatctat ctatttaato	1320
tataatctat catctatcat tctaattatc atctagctat ctaatctatc tatcatttat	1380
ctttgtttct atctatcatt tatctttgtt tctatctgtc tatcaatcat ttatctatgt	1440
atgtatgtat ctatccatcc atctatctaa tctattatct atctatctat ctatctatct	1500
atctatctat ctatctatct atctatctat ctatctacct acctatctat ctatctatct	1560
atctatctat ctatctatct atctaatacta ttatctatgt atcttcatgt atacaaagat	1620
atataaatac agtgtgatga gtgagctcat tttcttgttt gtatgtatat cctttcaggg	1680
atgaccactt tgcagtgagc aatgataagg tagcttatct ttgagaggtc aactctactc	1740
ccagcagtca tttgttgtct acagttcttt gactaggggc agggctgtcc aaaatttgaa	1800
tggtagatga tatttatcata gatgtggtaa ctctcatcaa ttgtatacaa atgttgtatt	1860
ctgattaaat ggaagaatta tcaaatagat gaaaaccccc atctttttaa taagtccttt	1920

WO 2005/005597

PCT/US2003/027106

```

ccatccaatg aagtaaatca tgaagcaata aatgtagaaa catgagataa atctaaaaaa 1980
tatatggctt caacctgagc ccagtgcatc ttgaccagc ctgcccactg gcatccccta 2040
gggaggctcat gtgacctaca catgtgtgtc taatctcaca tctgtgttaa cagtaaaacc 2100
tctctccacc ctccaatccg cctcctctgt gatcccata ttctcctgtc cacactgttc 2160
cacccttctg ctgcaccacc caatggccca aaggccttat ttaattcagc taagcatttc 2220
ccatttttca agaaogagct tgc 2244

```

&lt;210&gt; 55

&lt;211&gt; 1511

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 55

```

gggtcaactgc agtgctctct ccttcaaaa gatccaactg atgctgaggt agaaattgaa 60
tgtcgcgccg ccataatctc cctctcgga ctcttgagg gatgtctctt cagtctctctg 120
agcaggcttc ttctgaacga ctgttgtgtg ccatttcta ggtctgcctc ttggcggttt 180
tttctccaat ggtctctgtc ttcttctggg ctgctttaga gggactcttg tttttgtctg 240
ctttgggtct tcctctgggt ctcttaggag agggctcaca ggagcttagg aggttggtct 300
ttgtgtctgc ttctgggtc ggcgcgtcc tcgcttctgt ggcacctggg cggcagggtg 360
cccctgggct gatgtggaag gctgcccgcg gccctcacg cgtgcgctca tcttgcctcc 420
cgccgcgctc accactgcct ccgcgggtac cgccactgca gccgctcggc ctccaccgcc 480
cgggacccgc ccagcacctt tcggtagacg ggatggagag agctggagag ggcgaagagca 540
gcgagagcag gcgagctggc gtgtgcgcct gggactgctg ctgcttaggc tgccgcgct 600
gccaccatcc tgcatcactg ttaaggggaag tggaaacttg agggttcttt ggaagtcgg 660
tgggatggtg ttttgcctgg gcaaacctg gaaggaatgt tgccgttgcc ttaaagtgga 720
cacagggtgtg aaaggctaag gcagactcct gaagaaactg tttgtgaag ctgacacagg 780
agagaggatg ttctgctaaa gcaagaaagg atacctgatg aagattctt cgataacaac 840
atgcatgtac tggtcagctt tacatttgtt agttgagctg tattttgccg ggcagccata 900
gagagaaatg caccaaaaaa cttctggttg tgtgtctcag cttcttgatg cttccaagga 960
ctcgggctga ttggcagagt gatgccagct gagacaggcg attgtgtcta ggcagggcat 1020
gtggaggaca cgtgatctat ggagggacta aatagaactt gacggacagt ggcagaggct 1080

```

**PCT/US2003/027106**

```
<210> 56
<211> 1219
<212> DNA
<213> Mus musculus
```

100/186

WO 2005/05597

PCT/US2003/027106

```

acattccggt ttgtctttt tccaaaaaa aaaaaagaga aaagaaaaga aaaaaaaga 960
tccaaaaggc tgcaccttac acctgaaggt cccacacagg ggacatgaca tcttgccagt 1020
aagagaatga atgacagaaa aggaagaga gaaacgcacg cgcgcacact ctaggagcat 1080
ggcagattca ttccaaaaa acagtattgg ggggtggatg ggggactggt ggaggttttt 1140
cttttttttc tttttcatag ccccccatat tgtgagtaac tgccaccaca ttctctcagc 1200
atcaggaaac acagccacg 1219

```

```

<210> 57
<211> 4491
<212> DNA
<213> Mus musculus

<220>
<221> modified_base
<222> (3755)..(3755)
<223> a, c, t, g, unknown or other

```

```

<400> 57
agccatctgc gaagttcctg gaggagagga agaggtgaag agttaggagt tgggcactgg 60
ggagtgtctg tagtcagtag agcacttgct atgcaaaata aggatctgag ctccggtccc 120
taaaagccat gggaaagccg agaatgtctg tgtgcatctg taacctcaga cctgggaggc 180
agagacaggc agatgcctga gttcgtggc cagtcagcct ggctgaatca atgagttcta 240
ggttcactga gagaccctgt ctcaataaa agtaaaaggc tgagtgtatg aggaagacat 300
ccgatgtcaa cctctggcct tgacaggagt gcacactcac actcctcatg cacaagttca 360
tgcacatgtg aacacgtagc acacatacac accagcatgc acaagtacac acacatatgc 420
acacacctgc aaggacaccc aggatcacia gtacatacac acaaacagac acacacatgc 480
acacaacacc cctacctgca ggtacatcca cgtgtacaaa cacacacaca cacacacaca 540
cacacacaag aactcctcaa actcagaaat ccacctgcct ctgcctccca agtgctggga 600
ttaaaggcat gtgccaccat gcttagcaaa agttgaagaa tataaaacca taataaatag 660
aaatgattga gaaaataaaa tcaacattga atatcatttt attaaataa acaaatcaga 720
agccattaaa gacaatcttt taaagataag atcacagtta ttttctctgt gctatgttca 780
ggatgggctt tctggagcag gtggaccaga agtgatgggc aaacttcaga tgggttgagg 840
aaggagggga gaggggtgat tgaagtcagg agaacagggg acccacaana cagcaagcct 900

```



WO 2005/005597

PCT/US2003/027106

gtctgtaaag cagagagagc attgggatga cagagtgcgc atttggccaa attaaccatt	960
ttctcaaaacc atagttgcac aattaatttt atctcagttg acggtgaetc cgtccttttt	1020
gttgctcagg ctgtgaaacc ttagtcagtc ttggcttccc cacccttcat ctgccaggct	1080
ctttttgttc gtggaagct cttttgccct ctgagtcac ccgctgccac ctagaccgtt	1140
ggaaaatctt gtatctcctt ttagaccata tctggagcct gactgcctct cagccctcc	1200
actgctaattg gctggcacia gccaccacia cttctggtct gagttgctgc acagtcatec	1260
tcactggact gctaattggc tctctgcctt caacagcagc acaccagcca gatggagcct	1320
catcgagtgt acagcagatc atgtcacctt gttaaaacc ttgtgtgact gcttaaatga	1380
ttgcagagta aaggtcagcy catctgctgt ggctctgggg tggcgacacc cctgcacctg	1440
ttcctctctg acctcatctc cagtactctc ccttacacag ctccagccac actggcctca	1500
cgcagcacc cctctgttca aggtctcagc tgtgctctgc caagactggt cttgtcccag	1560
agagctgtgg ggtaatat ttgtcacatgc cgtcttttta ttgaagcctg cctttgtcct	1620
gacgctgaaa attgtgcctg ttctacttta ccacttctac tgcctcagcc accttctcct	1680
actgggacga taacctctac ttcccatgga aggtcgtgca atgtcctca ctgctacatc	1740
agacttcctt cctgccttac agagaattca acatcctggc ttgggactca cacaggteca	1800
gaaatagacc tgctctctgt cagtgcattt catggcaaat gttgaacaca gtgtctgctg	1860
tggtctgaat ggaagaggac atttctctag tgggattttc attagataaa ctcatgtttt	1920
gtcacttaag gcttatataa atttgactct ttaggatatg aaacatctta ttaaacagaa	1980
tttatgtttt gttctatttt ataaccttat gtattgccac cctgactttg acatgatata	2040
ttttgaaaaa tgtatgttta tgaccatata tatataatat gcatattttt tcattttctg	2100
ctaaacattt tttttattct ctaaggattt gaaattagca aagtaaaagc aatctgccta	2160
gaaatgtaca ttaaaatcgt aactttccca ttttgtggct aagtgcctcg aggtctggga	2220
ctgtctgaa gtcactcttt tggtggactg tgagttagtc ctggtcgtca caccctctga	2280
agatcaatga tctcttacc aagatcacct tcaaaatgcy tgtggggcga atgtgcagct	2340
agccaggtta tatttactta ttagctggca ctagctaata aagtgggggc aaacaagacc	2400
aagccaccat ctctctggct ggctcacaga tggaaatgaga tttaatgtga aaatatatg	2460
aacccatttc tataaagctt tggcagttca ccctctggca ttagcattga gaattattaa	2520

WO 2005/005597

PCT/US2003/027106

ttaccaccct ggttcacgct gtgcataatgt gtctgttttg taagatctaa tgagggaagt	2580
ttggatcaag tacatcaaat atattcttaa gaaaggccaa tggtaggttt taaaatctac	2640
taacccaaag aaacacgagt gggacgatgt taattagatc aatgtagcca ttccataatg	2700
tctgcaacat gttgtagacc ataaatatgt attctttttt aatattttaa atgttaatta	2760
atttttaaca aacaacagct gtagacctg ttaggtaaaa ctgttttggt gggatgcaga	2820
atggttaacca tagtagccag gtcaggttgc tcagacactt gtgaggctgg ggacttcagg	2880
agagacttgg tcaccatccc ttttatctcc aggactaatg accctttttc tttttccact	2940
tacagtcttc agtgggtgca aaacggaagt caagttttcc catgtttggt gaagtgcaga	3000
cttgctttag gccagggata aattaacagt aaactcaggt tgaaaacctg gaccagcaca	3060
gaactgagaa ctcatgactt ttctaactcg ccactgtgct taggacgggg taattacaga	3120
gattttgcaa ctgttttata agcatttgaa attctagact tctactccca ggagatcagg	3180
gtcagactgt ttatgtctct catcagttga gtgagagtct ctttactatt ttaaatggtc	3240
ccctcatcct gccgtgtttc ctgataacca accttcacca agagctcgga acaggcagta	3300
ataattagac attaacaaa gacgggtttt taagctagtc ctttatggtt tatggtagcc	3360
agatttttag agctgttttg tatttgcctg gggaaaaacc gtaagaaatg ggaatgtagg	3420
atgaacatac tcaggtttac ccaagattaa agggaaggca cgttctatct ctattttaca	3480
attcactgtc ccagagtgtt ggctgtttgg aatgcagcct atgccctgtt ggcagggtt	3540
tggaatcaat ttacagtgtg tgagatgata acacatgttc tggatcaggg gcagggaatg	3600
ctggagactg taactctgtc tgtctcccat tagcacaaag tcttgcaaac tcgaagtctg	3660
agaagtgcct aaaaatgcta ggctcagaat gtatgtgtgc ctttacaaat gcaacacaaa	3720
acataggccc aggataaatg ccataaatg aagtnatca aaaagatgaa gacaaaaaaa	3780
ccacctcca tttaactgat ttccctggat tgggtagaga tgctactttt gtgaaccaga	3840
aatacagctg tatgcacatt gacatctgtg ctagtggtt cgataacgtt caacaacagc	3900
ctggagactg catctgagac tcaactcgctg gggagaaaaa actcggttga aagcgtctgt	3960
gctaataagg cacagcagta tgtgtacaaa attcagacag gttaagtgtg aacctgatac	4020
ccccaggcca cgaggtagaa gctgacctct tggctctaga agctaacaa tcaagtaacg	4080
tgtatgtgct tgtaagggca ggcttgggac aggcgccatt cagaagcctt tgtgaaacca	4140

WO 2005/005597

PCT/US2003/027106

```

aatggcaagg ctcagccaaa cgatgaaacg ctgcttcttc gaaagatgag atttacacat 4200
tgaaatgatc agaaaattaa aagttagatt tcttttttat ttaaactcta aaacctattg 4260
tgtcctggac ttttaaatga atgccttatt gcttttactt tacctgtaca catatatgta 4320
tatgtatgtg tgtgtgtgtg tgtgtgtgtg tgtgtatata tatatatata tatatatata 4380
tatatatata tatacataca tacgcacaca cattctctga tgatggctctt gagtaaatgt 4440
cagtggctat gtgattttaa atattcagac tataaaatca ttgcacaaat c 4491

```

&lt;210&gt; 58

&lt;211&gt; 2875

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 58

```

ggcggggggt gagttttect gtctctttat taggttgttt actaatatgt caggacgagg 60
aaaaaggcgc aagggtctgag ggaagggtgg cgccaagcga caccgcaagg ttctccgcga 120
caacatccag ggccattacc aagcccgcta tcggcggtt ggctcggcgt ggcgcggtga 180
agcgcatctc gggctctcatc tacgaggaga ctgcgggtgt cctcaagggtt ttccttgaga 240
atgtgatccg cgaacgcgtc acctacacgg agcagccaa gcgcaagacg gttacggcta 300
tggacgtggt gtacgcgtc aagcgccagg gcgcactct gtacggcttc ggcgctaag 360
cgagccctcc tgtgcctagg ccgttccttt ggcccgctt ccccatcca caaaggccct 420
tttcagggcc cacaagcat cagaaaggag ctgtggacat ttgtagttct cactagttat 480
gagcgtctca ttactttttg tatttggtat gctttgtctt gtatgcaaat tgagctgcct 540
gggtgcactt ttccattgga ggacttgagg tggtagggccc gcctaccgcc tgggacctgc 600
tcagaatgct tgcggatggg tctgcgtgaa tgagtttttt taggtgtctg ttgagttgac 660
agccccagag tgctagggtg cagcctctgc ggacgtctc aaaaggggaa aaagctcct 720
gtagagacag tggacctgaa tgagggcagg tgtggaggct tggaacccca caataaagtc 780
accctgtage ttaaaactgg cttttctcagc tgtagctgtt tctctgcctt aagcagctgg 840
gtttggggga agaggagcac toggatgtct accatttagt tcaggctggg ataagctctt 900
cgggtggtct tctgtttcag cttccacaga ccatatgtgt ctcatttaag tcttcagagt 960
aggttagtca cagcccttgc tgctccttca aagtacttgt attcgatgct ccataccgag 1020
atgggtttaa ctctggatcc aggaagtgc ttcccttaggc cctcggaatc aggtctgctt 1080

```

WO 2005/005597

PCT/US2003/027106

accggctttc tgtacacatt actcaaaacg gtagttttgt ttttcagatc tctaggtttt	1140
tacatctgat gtttacgggt cttctcactg gctgaagaaa taggagactg ttctcacagt	1200
tcttgaggca ggaacctggc atttcattaa gatatgggta tctcgtgttc aatgctttct	1260
gtgtggcaga aacttggtgc ggtctttcag cagatttatt ttaagtgtg atagtgagta	1320
cagctgtgga tgagacaacg aaggctaaaa ttttgagcgc tagatttgaa ctctgctctg	1380
tgcgatttta cacaacctcg ttttatgtgc cactgggtgtt ttgtttgtt tgtttgtttt	1440
gttttgtttt gttttttgtt ttgcgagag tctctctgc cctgtgggc tgacacttca	1500
cttctagagt ctgagcatac ataacactga taccattagt ctagtgaact cattttctta	1560
aagcaagtga aaaatgagat gtttattttt ctgtcttgag aaatatctca gttcacagta	1620
tatggttttt attttcttat aaagtcacat gttctatcaa actatgaaac acaaaatgta	1680
ataataatga ttatcacccc tcttttaac tgaattttga ttatttgaga taatcaaaca	1740
tctataacta ttactagcaa aaagaaatga aacaaaaaaa tgaaacttaa atatcattta	1800
ttattacaca aataacaaca gcaacaaaag tattttgtgca ttctactgtg aaatcatttc	1860
tctcaaaagg cttaaatag aaactgccat gtcacctgcc cggatggaaa gttacttagt	1920
ggtaagaaaa acagaaatct tacactgaca agatgatgga cgggacagaa atcactatat	1980
taagcaaaat tgtgtgggaa gccgccctca catttgccat tataagatgg cgtgcacagc	2040
tgtgttctaa gtggtaaaca taatctgcac acgtgcaggg gcagttttcc cgccatgtgt	2100
tctgccttcc tctgtgatgc aactgggccc atgggctgca gccaatcagg gagtaatacg	2160
tcttaggcgg aggataatcc tctttaaag ggaacggggt ttgcattct tgttctttct	2220
cttgctttct tgttcttgtt cttttctctg ctcttgttct ttttctttct cttgctttct	2280
tggtcttttt ctctctcttg ctttcttgtt ctttctcttg ctttcttgtt cttgtctct	2340
tgcttgcctc tgtcttttct ctctcttgtt cttgcttttt ctctctcttg tcttctgtt	2400
ttctctctct tgttcttgtt ttttctctct cttgttcttg cttttctct ctcttgttct	2460
tgctttttct ctctcttgtt cttgcttttt ctctctcttg tcttctgtt ttctctctct	2520
tggtcttgtc ttttctctct cttgcttttt tgttcttttt ctttctctct cttgctctct	2580
tgcaactctg ctctctaaga tgtaagcaat aaagttttgc cgcagaagat tccggtttgt	2640
tgctcttctc ctggccgggc gcgaacgcgt gtaagaaaat tggactctga aagattaaaa	2700

WO 2005/005597

PCT/US2003/027106

aaacaaaag caaaagaaat gtgttttctt c gatgtagag ttgtgtgtgt gtgcattgtt 2760  
 tgtgtgtgtgt tgcattgttt gtgtgtgcct gtgtgtgtgt tgcattgttt gtgtgtgcatt 2820  
 gtgtatgtga gtcattgaaaac tacaagaag atgctagagg agatgaaata aatac 2875

<210> 59

<211> 3560

<212> DNA

<213> Mus musculus

<400> 59

catttagttt ctgaggacac aggccttggt ttatgtcaaa ttaagagtg atagtttttt 60  
 tttttttttt tgccttaact tgtctagctt ctagataatc aagacagagg ctattagatt 120  
 tattcaacaa gcccttaaggc acaataactg agcagatatt aatctattct aacctcttaa 180  
 actaatctag ctactttcca gcccaaatc ccaatatact ttagtatttt tagtattgat 240  
 tttaggattt taatattgat ttggctctct ctgcctgctc catttggttt ctcatgggta 300  
 ctctgggtcc ctaccacact ggagaaacct ctctctcttc ttccactacc cctgccttgg 360  
 cggggactgg aagtcacgcc ctgtcatctc ctctgccacg tgattggctg atcagctttt 420  
 tatccaccca ccagagctaa ttggggagca gtgtttacac aacgctgaga caggagatto 480  
 ttagaagaag cactacaatg ccattgtogga attgcaacaa gatattgggg ccccgaaato 540  
 agtatttgaa tgatacacgg atagtctgta cacagggcac aataacatta tgccaacagc 600  
 ctgtctttta gaccactagc caaaaccagc tctccaagca tctgtggtct gaccaaagcc 660  
 aggcaactgt gctcatccat ctacgatac ttgttggtgg cctagaactg gcactctgcc 720  
 tcatcatgat gcaaatggta gtttcaggga ggtgtgcttt ccacagagtc atttgcttat 780  
 acaacctagg aggtgatgag gagatggaag ggtctggtct ggggtgggtg ggtctgtgta 840  
 ctctgaaagg ccagtgtgtg ttcggagggtg gacagcacac ctggagctgc actgctggaa 900  
 ggctcagaca tctagctgga ggagatgatt ccaattgcac tcgccacttt aggtctgtgt 960  
 ccagaaatgt aagaagcgtt ggaaagtgtt agggttcctt tgtgtccaa gctctctggt 1020  
 tctaacctgt actgacttgt agaccatgtg aatgaggctt tgaagggtgc cttagagatg 1080  
 ttttcattcc cagaagcttg gtggttctgt ttgagttgct tgtcagggac agtcagagat 1140  
 gacagtgatg tacataaaa cagagtttat ccatctgtca ggtaggagtc cacagtgga 1200

WO 2005/005597

PCT/US2003/027106

gctgtgggaa gtaaggact cgggcacttc ctgtgacatt ctgccaccta agcataggac	1260
ttttagtgta ttgtcagtat ggctgttgat ttctgaacc atccctggg gagtataact	1320
ctgggctctt tccagtagag gttcctgctt aatcctgttg tccagaaat agtcacatgg	1380
gcacaaggta ggtggcgaaa tgtagcgctc accccagcaa gcaatgaacg gtaggctcagt	1440
gactgtgggc aaagtaaag agatcagatg cgggggtgaac acttacttct cctcactag	1500
gatcttcagg acattcaaac cttactggcc cttaatgtgg aggtaatgg tgcatgtgc	1560
ccagacagtc ccgaagcagc ttctgatag ccgcaggaat tgaggccaag tgtcactacc	1620
atctcagcat taagactcag atacattttt agagtcccct ctctaaattg ctctatatac	1680
tgcttaggaa acacttaggg tgtctgtgaa ggtgcatatt cataagtgtc ctggcaatta	1740
acactccacc caccctctct ttctctctct cccctctccc ccttgtcttc ctctctctcc	1800
ttccctctcc ctccctctct ctctctctcc ttccctctcc tccctctct ctctccatctc	1860
ctcatgcctt ctctctggcc taacagcaaa cacgatattt tcactttaga agacagtgtg	1920
ccctgagagg aataaaaaa attttcttcc aacctgatgg tgccaaactc atacagaaac	1980
aaaccgaccc ggcattgaga agttgtctag catgcacaac agttcagggc atagcagaag	2040
cctagatcca gtgtaccagt gggaacagga cagaccagc cttgccccct gagggaggtc	2100
tagaatacct taagtcttga atccaaagcg gccacatctc acaggtctta ggagtgtttt	2160
tggtcattca gcgttttgct ttctcttgac gcagctgtgc tcagtaattg ggtgtccgt	2220
ttttagtga gtctcaccat tagcattctg catgttccaa acttcattgg gttttgatgg	2280
gcccattctt catacaccca ccggttcccc aacaacaca caggcagaat ctatgaatct	2340
acattaaaaa ttgtgttaaa ggcgggctga gagcaagtgt ctacctgtac tgaattgtatt	2400
gttactaata agaattaag gtctggagat ggctcagcta gtcaaagtc ttgccgggta	2460
agcctgacta catgaattcc acttgggtat agtgacaagc ctggtaactt ctgggcgcgc	2520
atctctcaat agctgcaatc ttgacaagtc accatgttcc tcgatatccc aggttttagt	2580
ttcttgaggt acaaacagag gtgcctccca tgtgtctatt ggagaactgg cctgtgtctc	2640
agggctctgt tgggacagat ccagcctgca tggctcagc gacacacatt tcaattgtac	2700
atgcatgtgt gtgtctgtgt atgtcttggt gtgtgagtac gtgtgtgtgt ctatgtgtac	2760
atgtgtgtgt atgtgtgtgt ctttatgtgt gtgtgcatat gtgtgtatgt atatgtgtgt	2820

WO 2005/005597

PCT/US2003/027106

```

acatgtatgt gcattgtgtgt atgagtgtgt atgtgtgtac atgtatgtgc atgcgtgtgt 2880
gtgtgtgtgt gtgcattgtgt gtgtgtcttt atgtatgcatt gcattgtgtgt gtctgtgtgt 2940
atgtgtatgt atgtgcataat atgtgcattgt gtgtgtgtga gttgtcattc cagttgatgt 3000
ctaggagttc cggaatgaaa ttagagaacg tagcagttgg atttgtatat caattctgtg 3060
tggaactcgt ggccaaagag gcagccctga ggaattgtgt atgtatgact ctgcattgtgt 3120
gtcatctca gcacttgatg gcagcaccga ctctcaggac ctgtctcaga catgtagatg 3180
gaggccacgc cattggtgct ttaaccagat gtgcagagga cctgaatgtg cagtattagc 3240
atctgagagc tggcaccac ctcagacctc attggatctc atatttcctt gtggaccccc 3300
tgccccctt ctgactcagt gattctggac ttcagctcag gctgagactt taagtaggac 3360
tgtgtctgtg ggagctgggg aggtaggata gctcagcagg tagagtgtct gctgtgcaaa 3420
cctgaggac ctattcaggc atgttgcttg tgtttataat accagagcct tggcatagga 3480
gacaggtgaa tccttgggtc tgcctggccg cccatctcac ctaatgtaca gattccagtc 3540
caatggaaga gctgcctcg 3560

```

<210> 60  
 <211> 2334  
 <212> DNA  
 <213> Mus musculus

```

<400> 60
taaaaaccca aattggaact atctctccc ttaccocctt tccottaatt cctattctga 60
tgacactttg gacatgaatt caaggggacg atgaattttt ggcattgtgt tttttcttac 120
tcaaatctg tttattgggt tactgcccc ataaaaagta aacatgactt ttaagtattt 180
ttttataaac agctcaatat aaaacataga cagtgtttga ttattttcct tgttaagtt 240
tgatttaaaa cgttggaat gtgtgtcttt tagtgtttac taaagtata agaaaaataa 300
gcattcaata cactatagat tccaaaacat aacattgcac caaatagaaa tgtatatttt 360
attatgcaat gccttagtca taaactgggc tcaaacatc ctcagcctaa aacactgttg 420
tcttttaata tgcctccac ccaaggcct ttcctctcag tatctgtcaa acttgaataa 480
cgtctctctt ttactattac acacaggcca gcctattaac ctgtgtctta gaattgttgt 540
atatagttct ttaatatcc atagggtata tttttgaatt ttttggtgag tatttgttga 600
atttgagata gcatacagta gatgtttaag aaatagtagg aagtcgggtg agacggctgt 660

```

WO 2005/005597

PCT/US2003/027106

ttccatcaag aactcctagc actgctgtaa atatcatggt gcctactgga agggaaatgta	720
gatgctatgc attttggaaa taatctgcac ctgttaaacc tgcagaagtt ttttaaatgcc	780
actttaacac taatgcactg acagattcta aatattttgt gagaaatggt gaaatgttta	840
acctgatagg cttctctata aaagagtgtt ttgttttttt cctgcacca caagctgtgt	900
ttatcacttt acagttgcac gttcaacttg tcatagctgg aattactgta taaaagaac	960
tgattgtgac ttgtagtctt tctctagagg atgctgctag aacgtggttt tgctttgcac	1020
ttttagtttc ttccogtcag tgctgbtgtt agtctgtctt ctccagttct gcagatttca	1080
ctagaggcgc cctttgcacg ttgcactctg ttctcatttg gaggttggac tcagaccagt	1140
tagcacagta ttctctcaco tgtgtcactt tgtaaaacta actgtactct gtatttctta	1200
tttgtacata tcaatgtgag aaatctccct tttttatggt gcaattacct tgtgatcagg	1260
cagcttgagt gctatgcata tagtaagtag tgtagtggtg atttttcttt gcattgtgtg	1320
tgtgatatac ctagccagaa atagatgtgg cttttgtttt gggggcagat tactttcaaa	1380
agcaaatata attcacttga atttgacaaa ctgaagcaga caagtgttct gggctctctg	1440
ataatttggg gtgttttgct gtcagctagg ctcatgaagt ccactgtact gtaatgatgg	1500
tatttacctc tgtgctattt taattaccct cgcgtctgtg gaactgctga tttgagtagt	1560
gatttagcatt tagaaaatttt gtaatgtaga gttttagaga gagcactttg aaagataaac	1620
attttattat gatggtgcta ggtacaaaaa ttatagcatg ggatgtgaag aaaaaaatg	1680
agaaccattt gaaaggaaga aaggaatttg ttgtctgctt ctaagctaga gtggttgtaa	1740
aggttctgct ctgccagtgt tcagtatcag tggtgaatt atggataaga actgtagaga	1800
atcttctgtt tagtcogtgc tttttatgta gaattggttt tatctaatag ttttactatg	1860
gaaatcgctt ttgatatta aagccagatt ttagaggttt gatattgttg gtctcaggag	1920
ctcaaaagaa gtactgtttt ccagtgtctt ttgtgttact gatttgggaa atgttgaaag	1980
attggacagg gaagaatagc gcttggtgtc ctcatggtca ttctgtctta ccttagtgge	2040
ttgacagtac ttactatagc tctgagggga agccaatcaa cttctgtttt cctacctgac	2100
ctgcagggca tgatggatca gtgatgaaag aattgtagcc tgtggcactt tgttttgacc	2160
tctggtagat aactctgact tttatagttt taaaatgac aatctttgta tgaaagtcag	2220
ttttctttct ttaggtatca gaagattttg ccttattctg aggtcggact agggccaagc	2280



WO 2005/005597

PCT/US2003/027106

aagctttttc cttcatgtga gctgtcatac tgtattttga cctctttctg cacg 2334

<210> 61

<211> 4052

<212> DNA

<213> Mus musculus

<400> 61

atggaaatga tttttctttt ttccccatt tgggatgatg ttggctgtga gcttctgtga 60

tattgcottt ttttttaggt taagctatgt ccctgtatt cctagattct ttgggacttt 120

tctcatgaaa gtatgttga ttttatcaa ggtttttctc tgtctaaaga gataatcatt 180

agattttcat tactcagctc atctgtgtag tagattatac ttatttctat gtatgaggta 240

gattacattt atttatgtat gtatattgaa caatctctgt atccctgggg tgaactgac 300

ttcattataa tgggtaactc ttatgatgtg ttcttgaatt cagtttgcaa attgaaatgt 360

aaacttaagg gtttttttga aagtcagttg tgttgatgg tattttcttg gagcaaacac 420

ttgaaggagt attttactga agcagacaca gatgaaagga tgttttgcta aatcaagcat 480

gtgggacatg tgaaggatcc atcactaatg agatgcctat attgatctga cttacactgc 540

acagctgagc tctgtttgtt gtgacttcat agaattgcac caaaaaaact aaacaaaaca 600

aaacaaaaaa aaaaacttta ggctgattgg caaagtgatg tcagctgata cagattcaag 660

tgaagttttg ctaagtcaga ttcacatgct caggcaagat gtggtgaggc aagcaagacc 720

catgaaggac atgtaatact tggagggaat gtaagtagga ctcaacaggc tgtgagagag 780

gcttgggtag gcttggcttg cttgctagta gagctagctg tacaaatcat cttcacatct 840

tcactgagag aggcacagcc aagaacttct gccattcccc ttggccttga tcttctctgc 900

ggaatcgtgg cgattaggct gaggcctggc tgtctctgct aggtcatgct accactgatg 960

attcaagttt gctattctga ctctattgaa ctagctgggt tgttggtata ttcatgaagg 1020

atttgcaagt ggattgagct gccattgctg agctgaactg aactgctgat ctctcgacaa 1080

tgcagatggg atttgctcca aagaaccatt tctaaacagg tgcacccccc cccaccctcc 1140

atccaacccc ctgtatcctt tcttttctcc gacctctggg ggggtggagg gtggaggactac 1200

aaagaaagtt aaagggttta agaaccaaca ttaaaagtag gccctgaaaa aaattaacat 1260

tattctaagg ggtttttatt agagtttttc cattcaattca tattttatcaa agagattgaa 1320

WO 2005/005597

PCT/US2003/027106

ctatgattct	cttttgtgta	taaggaggtc	tttctctgat	tttggataaa	gggtgatact	1380
ggcattgtaa	aaatgatgaa	atgtccttta	atttcctatt	ttgtggaata	atttgaggcg	1440
tatttgtatg	agttcttttg	aaggtgttag	aaatctgtgg	cgaatccatc	catctggtag	1500
tatgctgttt	tgaattggag	gattttaatt	actggatctt	tctcgttgga	tgttatagtt	1560
ctatttaaat	tatttatttc	atcttgatat	agatttagct	tttataggty	atatgtatct	1620
agaaattaat	ttagtctttt	cagattttct	attatgttag	aatatagata	tttttaaaaa	1680
tattgtcoat	attctctgaa	tttctctttt	atataacttt	ctgtatatta	taagtactat	1740
taatttgaat	ccttcttttc	attgatttgt	ctaaagggtt	gtcaatcttt	tcaagaagcc	1800
aacaccttat	taaatgtatt	ctttgttttg	ttttgttttc	tatttcattc	attttcagag	1860
ctgatttgat	tgtctctgoc	catctacttt	gttttttttt	ttcccaagga	ctttgtgtgt	1920
attattaatt	tgagatgcct	tgcttgcttg	cttgcttgct	tggttaactg	cttctcttct	1980
ttcttcttct	ttccccaccc	ctcttctctt	ttctcttctt	tttcttctct	tccttctctc	2040
cttcttctct	tccttctctc	cttcttctta	gctgtagtgt	tatggaattt	tttttaggga	2100
cttactgtct	tcattgtgtc	ccatagattt	tgggagtgtt	tgttttcatt	cagtagtttt	2160
aggaattaat	aaaattctta	atttcttctt	ttcttctatto	agttaacact	cagtgagatt	2220
ttattttatt	tctacaagct	tgtgaactgt	ctgtggttct	tgtgattgat	acatagcttt	2280
ataccattgt	ggcaagatag	gaaatggggt	gtaatttgaa	gtttgctgca	tatttttagac	2340
ctttttttgt	atcataataa	gtagttgatt	ttggagaatg	tttctctggc	tccttgagaaa	2400
ttattcttgt	gataattagc	ttaaaatcgc	atgtaaaaaa	aagcatacct	gaatctcttt	2460
gatacagatt	atgtgtgatt	acatcaaaac	actttataaa	gtatatatga	cactctccat	2520
aaagataaat	tttgtagatt	ggtagaaaat	tcctgtagct	acacatattg	aaacaaaggt	2580
caccaggcta	gagagcacct	ccagtcacgc	cttctcagta	gaaagggggc	tttgcatctc	2640
ttctctgaaa	gaacatccct	gtgtgcttga	tattctgggt	ttccagagta	catatgtgta	2700
agcacaaa	taacctctga	tttaatgcgt	agttttgtta	ggcttagtaa	tcttgtttga	2760
aacatgggat	tgttcaggac	ttggaataca	tgcaggctct	tctggcttta	atatgttcta	2820
ttctaata	tgtagcttta	tctctctcat	agagctttca	gtgctctatg	agagctcttt	2880
agtcgtgtgt	cttaatatatt	gaaccataaa	atatgaatta	cttctctctc	tggactgtgc	2940

WO 2005/005597

PCT/US2003/027106

tatttggtat tctgtaaccc tgttttgtag ctatagtagc ataatttttag gtttgggaaa	3000
tagtccttgta tggattttact gaagatatcc tatgcatttg ctgtagcatt ctgtattttc	3060
ttttatgcct ttaattcagg aagttgaggt ttggtttttg ttggttttct tctttctttt	3120
tttttttttc cttttatccc cagtttatag aattttggcc ttctgatagt ttgggttgac	3180
tctctgtatt cttttggtat gtgtttcacc acttttggcc ttggtctata ctggtttttg	3240
ccatgtgctc aatttttatt tggcttttta cattgtagag ctttgggata cattattagg	3300
ttatttatta gtgtgaacac ttccagccat aacctttcct ctaaggattg cttaggtatg	3360
tcccagaggt tctgaaaagt gttgttttca ttttcattat gtttccattt gtaagacct	3420
ccaaggttcc ttcagtttaa aagtggtgct ttccagtctc aagtatgttt tctgaggtta	3480
tcattgtttt tgattttctag ttgtattgta ctggggctcg acagatgcag gaatcgtttg	3540
cttttccttt cctcttcctt gcctccttcc ttttgctttg tgtttctcaa tgtgttcaa	3600
agagtgtcat gtgccactga tgaactgca ttatttatct gttaggtgca atgtttgtag	3660
ctctaccaag taagtttagt tcacctgtgg tatgacttaa ccctaaggtt tctttgttga	3720
attttttttg actgttgttt ttgggtggta ttgggggttt tttgttttct tgagactggt	3780
tttctctgtt taactttggc tgccttgcaa ctcactgtag agtagggtag atctcaaaact	3840
cccagagatc tagctgcctc tacctcctga gtgctgggaa ctaaagggtg gtaccaccac	3900
ggatgggtct tgctgaattt gatttggagg acacatctac ctagtgtgaa agtgaggctc	3960
tatctccagg cctctgcagt gatgtgtacc gtttaatgtc aggactcaga aaatatgtgg	4020
accocataaa gcctcagtg gtcttttgag cg	4052

<210> 62

<211> 1815

<212> DNA

<213> Mus musculus

<400> 62

agtttttact tattccctct tattgagact gttagtctg acctagttag ctgcattatt	60
tattccctgt tagatcacag catggagtcg ttgaaatgat accttcagtc agcgtcactt	120
ctttccacag tgcagaaaag tctggaaaac ctcaggcacc ttgagattca gcctgtgtta	180
gggctgcagc ttgagaaaaa cacogtgtga ctctgaaaca tttcccogac ggctgaattt	240
ccttttctgg gttttcctcc gtgccacaag ctcaggacca agtgtaagaa gcagcccttg	300

WO 2005/005597

PCT/US2003/027106

1	aaaaatggca gcagggccta gcaatctcca gtgtgagcct tcctgcctgc ctcagcgtga	360
	catcggggga cactgaagtg gatgctaatac gtgtgggtg attccttgca cctgcgtgct	420
	gaccccgagg gaaatctgtg actagcaacg tctggccagt gtctgcctac ttatttcagt	480
	acgcttattt tccatcccca tagaaggaga aaaattagta gagacatttt attcactttg	540
	catttgtgta catatgtata aatttactct gagttcacgt gtgtgcatgt atgtgtgagt	600
	gcatgcata tcgtgtgtgt gcatgtatgt gtgtgtgcat gtatgtgtgt gtgcagtgtat	660
	gttcacgtgt gtgcagtgtat gtgtgtgtgc atgtatgtgt gtgtatgtat gtccacgtgt	720
	gtgcatgtat gttcccggtgt gtgcatgtat gtgtgtgttc atgtatgtgt gtgtgcatgc	780
	agaagccaga ggtcactggt gagtgtctgc ctgtgttgca ctccaccttg ccatttgaga	840
	cggggtctgt catcaaatct ggaacttaac aattgagata gaatggctgg ccagagagct	900
	ccagagatct tctgtctcca taaagcactc tgtccccccc cccccccca gtccagtgtct	960
	gtggttatag aactgcgaca caagcttttt atatgtgcac tggggatgca acccagttcc	1020
	cogtgattgt atggtaggca tgttactcac tgagccgtct ccctagcact taagtttacc	1080
	tctgaattgt tagactctag cgtgtctgta gtgaagagcc cattaaactag aggagtagtg	1140
	ttttcttagc aacctcaagt atggtaaaat gttatactgg ctagcttgca tcagagggaa	1200
	aacacttttt tttttttaac tttttgggat ttctatgac attatttcaa atcaggaaga	1260
	aaggaatttt ccttgtggaa agctaacatg gtttgaagta tttggctctg cattgcactt	1320
	gtctagagcc tgtttgcaga tcagagttta cgcagtgcc acacacatga tctccttcca	1380
	ttgtgatgat catcctgtaa aatgggtagg acaggaggca ttatctcctt ctaaggtgag	1440
	aaggcggggtc ctggaagatt aaatgactgg tttgcagtca gcaggcaggc aggtcctgga	1500
	agattaagtg actgatttgc tgccagcagg gcagaaatga cagaaacgat acagaaggga	1560
	tccaaactca ctctcttggt tttagtccc cttctcttgc atgatacagc aacaactcag	1620
	tacagtccag agatgcagtt tatttattta ttattttatt tatttagact cactgggtgtg	1680
	tctgtgaaca gtcatcatga gtctgtgtct ggcatagtcc ctatgagcac caggatttgt	1740
	gaatatcttt attttgacag gaacggaatc accactgctg tgtcccttaa taataaaatc	1800
	tgtatttggt tcacc	1815

WO 2005/005597

PCT/US2003/027106

```

<210> 63
<211> 1727
<212> DNA
<213> Mus musculus

<400> 63
gtcgtagacaag tccaaaagg gaaatagaaa atggagcatg ctgtagaata gaccttgaat      60
ggactggaaa gtctcttgtg aggagggtgg ccttatttaa ggacacaggg attttattta      120
aggggtttta aagtggagta ggagaagaaa gcagagaatg taatcaaggt tgtgtaagt      180
ttgactttga aaccaaataa gattcataag aattttcaaa aatagtacaa aggggtgttat      240
gtgtcttcac cctgtttctc ccagtcagag aaccttacac aatcataata tagtgttgaa      300
aatacactta tgtgtctgag tgtcattggc taagatgtag atatatttcg attttataat      360
ttatttttag ttaaaggttc aaaacaatgc atagaaagga ctgaagccat ggctggaact      420
ataaattcac aatcttagtt ggagattaag gagcaaagcc cagttggtag atgagcgatt      480
gtttgccaaag atagttagaa gggctaaaat gatgtctcag ttggtaaagt gtttgccatg      540
caagcacaaa gacccaagct tggattccca gcactcacia agaaagatga acatgatgg      600
gtgtgcctgt aattctaggt ctagggaagt ggagacagga ggagctcact ggttatccac      660
tcctgtctgaa ttgtttagtt ccaggttcaa caagagactc tatccaaat tataaagtgg      720
agagtgcacg agaaggacag ccgatcaggc atgcacatgt ttgtatgttt gtgttatcta      780
tcctatgtatc tatgtatcta tgtatctatc tatctatgta tcctatctatc atctatctat      840
ctatctatctc atctatctct gtctttcaca gacacacatg tgtatacaca catacatcat      900
acacaaataa aatctagatt actagaaata tttagaggtg gaaatgctct atatgtctaa      960
gtgactacat acttgtgagg cagaagagat aaagtccaag gggagctatc agtcagtggt      1020
tatgcttcta actgagaact agaagagaag cagattttatg gaaaaccaag acactttcac      1080
cgtgatcaca gtgaccgcga gacacctgtg taggggatgt tcttactacc tgaagctcaa      1140
gaaagatggc ggctggagtt gggagggtta aaggttttag catcctacat gtatgggata      1200
ataaaacacc tggttaaacac tgtcactttc ctgtgattct acttaaaagt atgattcaaa      1260
gatttctctg ggggtttttt ggtgtgtttt gttatgcctt tgtttttaaa gcttagcatt      1320
tatattagtg taaactgaat tcatgataaa gtgtgatgtt ttctttaaca ttccctccaa      1380
aatgttgctt tgctttggga atacttaaat aatgtactgt ttaggttttt cctccaagtt      1440

```

**PCT/US2003/027106**

```
<210> 64
<211> 2314
<212> DNA
<213> Mus musculus
```

115/186

WU 2005/005597

PCT/US2003/027106

```

aagtatttaa ggtggaaaat taacatcatg agacaaaatg tcaccttttg ggtgaaaaca 1200
ctcagcgttt ttacctcctg aagtggcagc ccaattcttc tgatggatgg gtacacctgc 1260
tgctttcaga aaagcgttcc agtgggtcat gaagtctctt ttgaaaatt ctaaaatata 1320
cagtatgatt acacctgagg ctgcaagggt tgtgtgtgtg tgtgtgtgtg tgtgaatgca 1380
tttatatgct tatgtgcctc tgcatacata tgcatagaag cttgtggaac tgtctggact 1440
ctaaaaaaaa atacacatca tcatttttgt ctttgtcaaa cacaattctc aaaaagagtc 1500
tagtgaattt aatttaaaat tcaatgagca ttgttgggc acaatctgaa ctgaacagtg 1560
gaaaactgaa cagattgaga gacttaagga cttcaggggc cagtggacag atcaaccagg 1620
taaggaaata actgaagatc ggggttactg ggtccacgc aatactgtca ccagtagtgg 1680
taaatacaga ggacagagtt agcactgacg agtctaggag aaactgtaga gcaaatacca 1740
tagagaaggc tcatttttat ctaaccttga agaatacac cacttggaag tattatggaa 1800
ggaagaagtg gttaaaagc acagaaacca tgaagtagca tgaatatctc ataaattgct 1860
gaaggcagga gttgggagac agcccttggt ctgggttatg ggctcttgga agggacaacc 1920
gagaatagcc actattggcc acctttgtat taaattcaag gctgaaaaac tcaaggggtt 1980
gcagaaagtt tctgcagaag ctgcctatga gtctgttgct aggactgact tgttagtgg 2040
cagtcttgcc tcgctttcca ttctttcaag tgtggcgact ccagggaaaa taatctacca 2100
tgtgttaact gtgctgcacg atttctctt cacttatac aagtgcctaga catttgttga 2160
ctaacagaga gatgttagag agatggaaga tgggtgctta aggcatttcc agtttgtgag 2220
agattaggca taaacgtgca aagtactcac aatgtagggc ttcagtgaca gtgcatttaa 2280
aagtaatttg agaagattgg ttggaacaag ctcc 2314

```

&lt;210&gt; 65

&lt;211&gt; 3368

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 65

```

tgagtggatga gtgactcggg gcggctccaa acaagctgga gggcttggcc ccgccttcc 60
cttgctctgt ttttggggc ggtctagccc aggcctcatt ccacgctcag tccagctcag 120
tcacccctga gtcttcagtg ttccagatt tagcctgtta ctccaccacc ctcttacacc 180

```

WO 2005/005597

PCT/US2003/027106

tccactcatc	tggttactgc	ctgtctttgt	tactgagctc	ttcactacc	ccatccatct	240
aaaatactcc	cgaaggtcag	cacacttctg	caggggaat	ggtaagagac	agctcagcca	300
ggaagaatgg	agaaggctgc	ctatgccccg	gtagccatgg	tggatggcag	agaggtgtgc	360
cttggtccac	agtggttggc	ctagggcttt	tgtgtattgg	gtccatcttg	gtgggaaggc	420
tgagacaaaa	gaacttcagc	ctggagttag	ccaaagaaaa	gctgggcag	gtagtctcgt	480
cctgtagtgc	caggattcag	gaagggtggg	gattttgagg	cctgccagag	aggtacatgg	540
taaggtttgg	gaaaagggga	aggggagaag	gggtgtgtat	gggcagggat	ctaagacagg	600
gaagcagcgg	gacttggtat	gggcatcctt	gatggacggg	tgctttaggg	tacctttac	660
tcgtccttag	gaacaggtaa	tggggatggt	tagaggaggt	gggggtgggt	aaaggtccc	720
acagtgtgct	tcattgattc	tcttggtctc	ttgcagaaac	gggggatatt	tatatctggg	780
gctggaatga	gtcagggcag	ctggccctgc	ccacaaggag	tgggacagag	aacaaagcag	840
agagagagga	agccacagaa	ttgaatgaag	atggtctcaa	agaggaatta	gctgtggctg	900
atgcaggagc	tcctgccacc	ttcatagcca	tcacgccctt	ccctgctctt	ctggtcttcc	960
ccctgggctc	agatgcagtt	atgggccagct	goggatcccg	acacacagct	gtggtgacac	1020
gcacaggaga	actctatacc	tggggctggg	gtaaatacgg	acagcttggc	cacaaggaca	1080
gcaccagctt	ggatcgaccc	tgctgtgtgg	agtaactttg	agaaagacaa	cttgaagtaa	1140
gggctgtgac	atgtggaccc	tggaaatact	atgtctatgc	aatggaaaga	gacaaaagct	1200
gaactatccc	ttagtggatc	cccacttatg	tgcttggttg	ctgtatggac	caatgacagc	1260
cccattaaga	cagcaggacc	agagactcag	ataaaaaatc	ctgcagccgg	agctgtgaca	1320
aggggaagcaa	tagtttatatc	aaaacagcca	aggctgtcca	agtctctcag	agggaaatgt	1380
ctggacccat	gagaagagaa	agcaactttta	tgagattctt	atatattcat	attcaaatct	1440
tctctatgta	gcacaggctg	gcttccactt	tgactcaggt	tcctgaatgc	tggattatgt	1500
ttagagatta	aatctaggac	atcacgtatg	ctggtaaac	ctcctaccac	tgaactaaac	1560
ccacagtggt	gtagataaca	attttgcac	aatccacaag	atgtctggaa	ctccctgtct	1620
tgaactcctg	agatctgtag	attacagcct	cccagcaaat	gogattacag	actatactca	1680
agagatgaga	agccccacac	attacatgct	cagcgtttac	acagagaaga	ggccagtag	1740
cgcgcacttg	cggcggcgcg	tgagctcggc	cgccagctac	gccaggcctg	agacaaaccc	1800



WO 2005/005597

PCT/US2003/027106

a c c c c g g c c t	c g a g g a a g c g	t g t c a a c c c c	g o j e t g t c c c	c g t g c t c g c	c c c g c t a g t g	1860
g c c t c g g g c a	c a g a t g c c c t	c c g g a g c c g g	c t t c g a g c g c	c c c a g c c a c a	g a c a t c g g t g	1920
c c t g a a g a c c	g g c g a a c c c a	g c t t g t c g a a	c c t g g t a c c a	g a c c c g c a c c	t c a g t a a t g g	1980
g t c c c g c c c c	t a a g a g a c c c	g c a c c t t c t c	c t c a t g g t g g	a c g c t c c a a g	c t g t c c a g a a	2040
t c g a g a c c c t	c c a c t t g c c a	g c g c g g g a c	g g a g a a c g g t	a a c c a g c c g c	a g c a g a c t t c	2100
a c c c g g a g t c	c g t c t c c a c t	c t c g a g c c g t	t g g a c c c c g c	g g a a t t c a a a	c c g a g c c a g a	2160
g g c g g t g c c a	a a t g a c a a t t	g g t t a c c g c g	t c g c c a c t c	a c g g a g c c c c	g c c c t c g t c c	2220
c g c c c c t c c t	g c g a a g g g c t	g c t g c c t a g g	c c t g g g a t a c	a g a g a c c g c c	t a g g g c t g g g	2280
g a a g c g c t t g	c a c g g g g a g c	g t g c g g c c c t	c a a t a t g c g c	a t g c g t g c a c	c t a t g c c c g c	2340
c t c a a g g g t g	g g g t g t a g g g	g t g t g g c c g a	t g a t g t c a c c	g g t a c c c a c t	g a g t t g c t g c	2400
c g t t g g g t t t	c a a a t t t t t g	t g c t t c c t g a	g a a g t a t t g g	g t a g a c t g c c	a g a a c a g c t c	2460
g a c t t c t t g c	t a c t c t c c a a	t g t c c c a a g a	g g a g c a g g g a	c t a g c a g g a a	a g c t t a g a a g	2520
g a a a a a a a a a	c c a g g c t c t t	g g t c c t g g t a	c c t t a g t g g a	c a a g t t t a t c	g c a t t t a a t c	2580
a t t a g a a c a c	a c c t g t t a a t	a a t g a t c a t c	a c t a t c c t g a	a g a a a a a g a t	t t g a g t a g e t	2640
t t t c c a g a a c	g t a g c g g c c a	g a g a c a g g a c	a g g g a a a t a g	t t t g g g c t a c	a g g a a a a a a c	2700
t g a c t t g c c c	a a t t t a g c t g	t g a g c a a a t g	g t g a t t t g g g	c t t t g t t t t t	c t t g c a c a t t	2760
a t a a g a t t t a	g g t a a a t c a g	g a a a a c t c c a	c a a t t t g a a c	a t g a c a t c a a	a g t a t t t g t g	2820
t a g c c g g g c g	t g g t g g c g c a	c g c c t t t a a t	a c c a g c a c t t	g g g a g g c g g a	g g c a g g c g g a	2880
t t t c t g a g t t	c g a g g c c a g c	c t g g t c c g c a	a a g t g a g t t c	c a g g a c a g c c	a g g g c t a c a c	2940
a g a g a a c c c c	t g t c t c g a a a	a a c c a a a a c a	a a c a a a c a a a	c a a a c a a a a a	a c a a a a a c a a	3000
a a a a c a c c a c	a a g t a t t t g t	g t g t c c t t t t	c t t c c c a c t g	a c c c a t a g c a	t c t g t a t c c c	3060
a t t t t c a a t g	a t t t a c t a t t	a c c t a a t a c a	c t g c t a t g g g	a g t a t c t c c t	t t g c t a c t c a	3120
g a c t a a a a t t	t g t a a t a a a g	c t g a g a t g a a	t t t c t t t t t t	g e t a c c t c c t	c c a a a a t g a t	3180
t t g t a g a a g t	g t a a t t a t t g	a a t t c t c c t t	t g c g a a g a g g	t a c t a t t a a a	c c t a t c t t c t	3240
g c a c c a a a c t	t t a c c t g g a g	t a t c c t t g t t	a c c c a c a g c a	c t g g t g a t t a	g c a a t g c g c t	3300
t t t a a a c c a c	t a g c t t c c a t	c t a t a g c c c c	a a a a t a a a a c	a a a a t c t a g t	t t a t a c t g a a	3360
t t a t a a c c						3368

WO 2005/005597

PCT/US2003/027106

<210> 66  
 <211> 1763  
 <212> DNA  
 <213> Mus musculus

<400> 66  
 gagacttgag cccatcgga ggattgtgtt ctggggccct ctcaggcagt acctctggga 60  
 acaggggctt ggatcggtca atgacgaaca tctcgtgtcc atgtgtatca cggagctcct 120  
 cgagctgtgc aaaggtgcaa ggcccatcgc aataatcgtt gacaaatagg gtgccttctc 180  
 ccgacggcgc aggcaccttt ttccgcgcgc gtcggcgctgc gcagatcata gctgccaaaca 240  
 acagcgcggt gagcgccagc agogctatgg ctgctgtgat cgctgtctgc gttgctaggc 300  
 ccagggctcg gaaagccatg ctacctgcct catgctgggg ttcatgtccc acagggcgctg 360  
 tagctggggc ttgcgggtca ggtagctgct gtgactgctg ccgagatgag ttgaccagta 420  
 gatgaaaggg cactcgagct ttgccacctg cattggcggc ctcgcattcg tacttgctcg 480  
 cgtgagccag tgtgatgttg gtgaggaaga gcataccgct gccagtatct cgggtgcgct 540  
 gcccgcccaa gcctggcgcc ccaccttcca gctgggcctg ggcttgaggc ttaccatcgc 600  
 gaggtctggg cacctttctc cagaccacca ggggctgttg gtagcctgat gctgacagg 660  
 cgacctcgag gtccctcccc agattagctg taaactccgg gggctccagc ttcacagagg 720  
 ggggaatgca gataggcta ccaccagata cttctagtag actctgtagc gccaggcgctg 780  
 ggggctctgc acatgtgatc ttctgtctc tggagctcag aagccgtcgg cccctctctt 840  
 tgatccaaga gccacgccag tgaagggcac agtcacaacg ccatgggttc tctgtgtagg 900  
 gcagaataga gcctaggtag atggatccta ctaatccaaa cagaagccct tatctatctc 960  
 ttacagatgc ctatagggtt ctagaacctc gtccacctct tccctcactc caacttccta 1020  
 ggaatgtttg tgatgacagt tccgaaaag gcgtcagctt ctctgtctct ggctttgcaa 1080  
 gcctctgcat ccctcagccc ggcaactgaaa cctgtctgtc acatgagctc tgtccagttt 1140  
 tgctcggtc cccctgatga caagttagaa gagcctcaaa tctctacaca cagcgttcta 1200  
 ggacaaccag tgccctcacag aaaactctgt cttgaaaaac aaaaacaaaa agagcttcaa 1260  
 ttctgttaag ttactctgca gaacttgtac cttgtttcct taaatagatg cataagctgt 1320  
 agctcctaac agtactccct ggtagtcctt tatcaaggcc gaggttcttg tgtggccctc 1380  
 caaagtaatg cccactggct gccatagtga agcaagacag acaaggggaa aatatagggg 1440

WO 2005/005597

PCT/US2003/027106

```

cacaggaagg gaggcaagtc cccatagaat ctggctgaag cctctcacca agtgacatca 1500
acattaactt tgaagattgc caacataaca atactccttt tacatttaga agaataattaa 1560
aacagcagtg aactctagga aaggcctcgg catgtatctg tggctcctcaa ggatgagctt 1620
gctctttttg taggtagtaa cgagactaaa cttttgttta cagtacgggc acgttccctg 1680
gcaacccttg ttacttggga gcatgcacta tctctgtat ccctacccaa tgtgcaggac 1740
ccacgtata aatgattcca ccg 1763

```

&lt;210&gt; 67

&lt;211&gt; 2324

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 67

```

aaaagccttg gaagaatcat ttgacctcgt agaaatgtca cacacttcaa gctattttta 60
agaatatatt tatttttaaat tgcacatgca gaagggtgat gtgcatatgt gatttggggt 120
gccacacaag gctataaaaag gatggcgggt cacctggacc tggctttaca gacatctgag 180
cagcctgagc caggaatga acttggttct tgcaaggaa gtaaacactc tttaatcctt 240
gggcctttct tctgctctt atcctgttct tgtgaaaaag tgaatctata caagtgtagc 300
acctctccta gctcatgtt ttttctgtgg ataaaaaaag ccgactcat catttttttg 360
atgtccttaa aattggattg cgggattggg caggatgaga aatttccat attgtatctc 420
ctttggtctt cctaaaggat gctaaatcta tctgtgcaaa ccataactgg agttagacac 480
tttgcctcgg ccttttcagg agctccgaat tctagaaaga atttaaaaga aaagattaaa 540
ttgtaattga atcaataaga gccagagcga taaactttta tatagagaaa tgagaattta 600
aaactgtagt aagaagtgc ccattaccct ccactattag ggtgatgaat taaccaatga 660
aagaattcgc taaagataaa ttatttagaa ctggattcct ctctgaccaa ttgtttaaaa 720
aaagaaaaag aaaaacacaa tactatcaca gctgaatgct cttctgggtgc ttgcttaaac 780
ctgagttata caacagtgtg aaaatgttgc ctcagggaac taaaatctat cactctgtat 840
tagatgatac ttcaatgact acccagcaa cattagatca aattagtgtc gatctaagga 900
aagtattatg tgcttagttt tgctcacttt acagctgttg ttcttaacctg cccatgggtg 960
tcacctgcag acttgccagc ctogaacttt aaggccaacc caaagtcagc aaatgcaagct 1020

```

WO 2005/005597

PCT/US2003/027106

```

gtcagattgt ttttcaacag cacattttta cttttgatgt cccttcaaac ataaaaataa 1080
aatatcttaa gcaagttatc tttcaaattt ttctactgaa tacatggaga atatgatata 1140
aaaaataaag tacttaaac taagaaactt tatttagagc aaagaagagt gcctcatctg 1200
gttcaactta aagacaactc tagocaacat gtctatgctc tcatcaatag gtacacttag 1260
aagtagtcat ttagttctac aaaaagatga aggtagagtc aaatgctcca gaccaaac 1320
gacaaacatt ttaaagggcc ctataactaa taagttaggg gactcataaa catgaaagaa 1380
aggagaggac tttctaaaga agtcatggtt tggtaacact caactacaca tctgctaata 1440
caatatgtta ataccgactt ttaaaacagc cattttaaaa ctgaatagaa agacaaactc 1500
atcccatatt attccaagga agttaataaa tagcaacta aattttatttc ccagaaacaa 1560
atattttttc tttttaagac tgtaacagtc atttctactga tgagcaactat ttctttactc 1620
aagagctagc tgtctcctct tgggttggtcc cttctacttt agctcaagga atgaatgtta 1680
tatttattca tccaaaagac agagaaaata ctttatcctt aattctatca ctgtgggatt 1740
actaaaatt gtctttaaac tcaaaatttt gagttaaaat catttctcct tggaaataga 1800
gaaaatacac ttttattctc aaacatactt tcagaagtta cacaaattaa aacatgggat 1860
cattagactt tattaacag attaacatgt acattaacat gtacatacca aaacacacc 1920
tagccaactc cacctaattt taaaaacttg aaaagtcttt gcctcttcaa atatgattgg 1980
ataatpactg caaaaataaa ttttactcca agagttaaaa gttaaagtag taacatttg 2040
agctggatga aaagacaata cagattttgt tctacctgtg agagattgca ggctgttggc 2100
catcttttaa gccaggata tctcatgta aatatgcaa tctctagcc atggtttctg 2160
caatatgaca aagttcattc caagagacca cattagcctt aagaaagtct gacagtgagc 2220
cctaagaaa ggagaggtgg gagggaaata ccataagct cttgatcaca atttcacata 2280
aacagaaact tttctctgga tataaaagca acacattcct ttcc 2324

```

<210> 68

<211> 1378

<212> DNA

<213> Mus musculus

<400> 68

```

tttgttagt tggtttttgt gtcccatcc tgcttccag cctcttgcat cagtctccac 60
cctttagcca tatgctgtac cgtagtcatt gttttcttcc tacoggtac aacatctcac 120

```

WO 2005/005597

PCT/US2003/027106

cacgaaacag cagcatgggg ccagcacttg gggcccaaaa gcoctgaagtc tgaagaggaa	180
ggaagcggca gtgcaagcgt cactgcagag gagcggggt atgccagtc acagctcctg	240
gccttcacct cgaggatgaa gttgaaggcc acagagacag atgcacactg tgcacagaag	300
aaaacacagc agatgccact ttggagaggg caagagaaa gaataaactc tatttgataa	360
tttatattag gaggaagag gactgaagat gttctgtgta ggaacagaag aacggacagc	420
atttctgtta gtcatcttct ggaaaagtaa tattttaatg ggaattatg gaaacaatct	480
aaatgtccaa ttgctgtgct agggtaggga ttattttctg ggaggtgtgt gtgtgtgtgc	540
gcgcgtgtgt gtcccacaca tggctttcta ctctcccaga gggcaagggc taagtgtggg	600
aaatagtgtg gagcttagct gaaggacagc tgtagacaa agcacatcca ggagccccag	660
gtgtcactgg ggtctgggca gcccccgaat gagatggggg aaggtattgc tcatgtctct	720
tcagaaagag tgctgaagc ccaggctta ctctattgct cttttagttt gacatgggat	780
ttggattttt tttctttttt cttttttttt ttgtttttt gtttttttgt tttgtttttt	840
gggttttggt ttttgtttt ttttgtttt gaaaggtctg aaagtgaac ccttcaactaa	900
atggcaaaa aaactgtctg tgtgtctcca gtccctcct gtgtccatct ttgtcctctc	960
cctgtccctt ccctgtacc ttcaccagc ttgtgtatgt aagctctgca ttcagacagc	1020
tgcagcatc cgaggttgga aatgtcactg attcttgac cttagaccag ccaacagggt	1080
taccagttc ctccctcag taccacttc ccagctatag cccagctctg catgagaatt	1140
tgggtgtttg aatgtttatg actctctcgg oggggttct cgccttgcca tctcactgt	1200
ggggaatatg agaaggggag gagaatcttc atcaactggt tttgtgtaat aaactttcgt	1260
gttttgtttt gatttgattt gatttggggt tgtttttccc cctgtctgt ctgtctgtgc	1320
aagatctgca gctgtgaaa tcagctttgc ctttaattaa accgtgttct ctccaagc	1378
 <210> 69	
<211> 3137	
<212> DNA	
<213> Mus musculus	
 <400> 69	
attttaacct tgtaatatga ctaatttgaa tgggtgaaa ttattttatc atgtaatgtc	60
attttcacct aaacagtaca attaagatat ttaaaactaa agatccaatc attttacaaa	120

WO 2005/005597

PCT/US2003/027106

ttcctaaaaa taagtgatag attttgata cactagtaca tcctccacat aaaaagtagt	180
tttgtgtatt tgaatgctca aaattttctc aagatgggat taaaaatttt ttttctcagt	240
tcctctgttat ctcatthtta atccctctct cctatgttct gctcagttac cgthttctat	300
ccaaattctg agtgthtct aggtcttggg ccttatctat ttcttttctt tatgcagctc	360
gcttcggagc acatctgtga gcttagaatt atgtacaatt aaatgtatac caaaaccatt	420
cacactcccc tttcctctca ttgcctgctc tagtatctta agggaaaata aaaaagctc	480
agtttaaaat atatgagtta aaatccctg agctgcagga tatgtgcaat aatgtcttct	540
acaaaaatca agctgtggat tatttctca cactcagagc ctaaatgttc attggagatt	600
taccattgca cttaagtgcc agaggaaatg acaaggtgac cattggaatt gttgtccaaa	660
cagaaaacct tgatatthaa gagaagattc ataaatctga agttatgggt ttctatgcca	720
gacaaatcag ggaacattac acttaggcta ctggagtaa ggctatttac gatttgtcac	780
ccacttcaaa aatttaatttt attttttaag attacaatat gattacatca ttctgcctt	840
cgattttctc cctctattgc ctctaataata gctccctct tagccctgtt tcggattcat	900
atatatgtat atatatatat gtatgcacat atgtatacat atatatatat atacatatat	960
acatatatat gtatgtgtgt atatatgtat gtgtgtatat atgtatgtgt gtatatatgt	1020
atacatatac acacacacac atatcttctg ttaactgtat gtatgttttc agagctgacc	1080
atttgccact agatgaactg tcagagtgtc cctccctggg gaggaactgt tcctccgctc	1140
ctcaggcttc cttagttgcc tgtggttctt tgtataggac taaggcattg tgggtttctc	1200
tgthcccttt ggcaagtctc ttgtttctct ctttgtttac ctctattta agcagctcat	1260
ttggtgaggc gttatgagtg cagcttggga cattcctgga gacatgaact ctgtcacttg	1320
ttttttaaaa agtcccttcc taaatatgca cccagcagct ctagggatga ctcatgggtg	1380
aaatccatat cataatctaa ccatttttgt cactctaagt gcaataatgg tgagtttgtc	1440
tattttaatt atgtacattt tgcatttttt ttacattta ttatttttgt atatgaggtg	1500
tgagcaagca ttttccacaa cacagatgta aaaattggag gacaattttc agaagctcat	1560
tttttacctt ccactgtgat tattgacctc acgtcaggcc aggccttaat acataccaag	1620
tcctctgggc catcccaata gccctatttt actaattttt ttaaaggctt agcaaatctc	1680
aactacaaga aaatattttc ttatattttc ttatattttc ttacatttc tgttattgtt	1740

WO 2005/005597

PCT/US2003/027106

```

gttattacag tttttaatat agccctctgt ggtgtgtgac tcttcctgga gagaaggga 1800
gaaatgacta gtcacctcag ttaggcaact gattagtcta aggaagtccac ccaagtccaa 1860
cataggaaga gccctagtaa atctggtctg tttcaggtac ttectgaagc gattaagatg 1920
tttacttcct gagtttaaa agtttcctta cagcatgtgt ttcaggatgt cacctgtttt 1980
gacatcttgt atcttaagga tcttccttca agatggaagt gtgtatttca gagggaatta 2040
gcacactcat ccagattgga ctctgaatcc ctgaaggagc tgcaggctac tgagcttctg 2100
cttatttctg ccacgctgac cactacacac gatgccgtga aacaaacctc aggetttagg 2160
catgttcagc aaacacttac caaatgtgct atatctccag ccccaataa agttctgcca 2220
ccttggtggt cctatggatt gaactcaagt cagtaggcag tgcagcaggc ctatttatgg 2280
actttcttgc tggctctcaa atgaattctg ataagaataa aaataagatt aggaacaat 2340
agtgctcttg taatttctca ctgtgaagta tcctgggtct ggagtggtgt gtattttcgg 2400
tagaaacatt tccctccac tgtcttccct acctgactct attaatactc aaactgtgct 2460
ttagacatag ttatgtaaca ttatgcatta tagaaatcta agaattgtca agatttgggc 2520
cttttcacat gtcccagtac ttagtatttc ggcaagtcct gctgggactc tcaaatgttc 2580
ttgaatttaa ggtttatgcg attctatttt gtcacctcgt cagggccagc caccotcaac 2640
ttttttctta gttcaactgaa ccaaagatt aactgctctc caagcatcca ctgcgacccc 2700
aaacctgctg tacatcttca ccaaagtgat ctttatttat tgaatcgcag tacttctctt 2760
ttcaatctct ctgataactt tctatctggc ctaaaataaa attgaaactc tccacagcaa 2820
agccactgag cacacagcat cactcaatat actttctgtc aactttctgc ttaatctctt 2880
cttatttctc agagagaaaa aaaatgaaat tgttattttg tttgattctt ttactctgc 2940
cctttggttg ttttctgtcc cctctaggat attacaaact tgtaactaaa cttagccgct 3000
gatatctaga aatgaataaa actcctacac acatcagaag taagcacagg gtgcctatc 3060
tgaaacacgg accaaagagt ctttccaaact tatttggaag aacaaagctg agagcagtgg 3120
tcagtatcat tttctgct 3137

```

&lt;210&gt; 70

&lt;211&gt; 2795

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

WO 2005/005597

PCT/US2003/027106

```

<400> 70
tttcagtggt gttcaaatca cacacattcc attatttgat tttagagagc acagtagata      60

ggtttcagct tccctagaga attctagaag gttcttggaat ggttacttca aacgaagaat      120

actgctgtac ctgagttgaa cagctaggga ttctctatat taacctggct tcggcacata      180

ttaaaatgac ctgacttcta tccaagggaa attcaaggta ttatgtcaag aatctaataa      240

atacatcttt actatcatgt cagagctaata agcacctctc taattgagtc tctctaattg      300

ttgctctgga agcttggtct tttgtttgtt tatttgtttg aattgtcttt tttttttct      360

gttttttttt ttttttgact tgtggtaaat aacgtgcctt tggtttgtct tctctagacat      420

tcgcagtcac gagtttcatt tgtattaaag agattttatt atttactgag tgggtgaagca      480

cagatctcac atatttttct ctcaactgctt gaaaggccct gctcaggcca ctttaaaaat      540

aaatatatta aaatttaccg tagcattgog aatgagtgat gtcacccaga gtgttactag      600

ggatggcaga cagctctctc tgaacacaaa gcttgacaag aagcctcaca gtgagagcct      660

cagcctgaag cattctctgc agaacctcac actgcctttg tttctgcctt ggcggttctt      720

tgtgcactgt gcataattcag ccactgggtg gcagtatgtg cttaagaata tttaatgttt      780

gccaccttgt tttagacagaa ttttaagaagt caggtttttg tttgtttgtt tgtttgtttg      840

tttttgtttg tttgttttgt tttttgcttt tcaatcttgc aaaaatgacca ttgtattgaa      900

tataagaagt acaagtattt tctgaatgca acagcctact cataaagtgc ctgaaaaatc      960

ttcttttaaa aatatattta atttgagttt tacagtttcc gaggattgaa ttcattgacca      1020

ccatggtggg agaccatgag gcagagagaa ctaacagggg atgggggtggg cattggcaca      1080

cttcttcaaa caagaacaca tatcctaate cctcccaaac agttccacct cctgggggacc      1140

aaacgtctga atgtacatgc ctatggaagt cactcttggt caaatctcca cagttaaaat      1200

gtatggtgat gctctgtctg gctttttctc aagatgttgg aaccagcta actttgtagg      1260

cctcctctct aagaagcttc tattgcagaa ttggggagtct gtaaattcta tcgaacaccc      1320

acacaccttc tccaactcat gggagtgggt ttctgacacc aggtcctagt actgacagga      1380

gacacacaca cacacacaca caaacaccca tccctaactc agacgtgatg ttactgatg      1440

accaatgcga aatgaaaaat cagttcttgc taatgaatca cagtggaaac acccataagg      1500

ccagccacca tgcccagctg tagctggcca acacaaaaa aagggaattgg cattgtttgg      1560

ggttctttga ctcagaaggt ttttaacaagg ctggggcatt gtttgtttta ttaccttgta      1620

```



WO 2005/005597

PCT/US2003/027106

```

ggctccttgc ataacatcag agcttcacgt tttctgtgtg cataaacatg tgtgtctctg 1680
catctacatg tgtatctcac gctctctctt cggtctcttt ctctgtttg tgtctttgtt 1740
ttgtcctgta tctgcttttg tatatacata tatacaattt tgtgtgtata tatatatata 1800
tgtatatata tatatatgog tgtgtgtgta tacatatata tgtgtgcgtg cgcgtgtgca 1860
cacacacaca cacacacaca cacagaatgc attcgggttg cctatctggc ctctggttct 1920
tggccactca agcagtgta gggatgggct ccattgcata ggctttaagt taaatcagac 1980
gagctttctg ccacaattgc accggtatat cttgcaggag aatcaacatt gtatgcaca 2040
gacttggtag ctggatttgg atttatcttt ctcccttcac ggcatgcagg gtaccccca 2100
gcaccatgaa cactagtctc taaagctgag agctgtgcgg caggctccag tgcaactctt 2160
ttgtgtctga taagccttgt aggtgtgtgc ttcagccctg gtgctcttac ctctctgtct 2220
gttgctgat gatggatttt tctccttcca cgatgttccc caaacgtcaa aatacagcca 2280
cagtgatata aggagctaa ccattagtct agcaccacaa cttctgata tttctgtct 2340
tacctaggc atgatacatg gatacgtgca gatgttgaat gtccatgcac ttaaatatt 2400
tctatcccca aagcagaatg agaccaatta atttgtctg aatataattt ctcttcagtt 2460
aagacaatgc ttccogacct tctcatgct tcaacccttt aatacagttc tccatgttat 2520
ggtgacctcc ccatcataaa attatttcat tgctacttca tacctgtaac tttgctaactg 2580
ctataaatca taatataaat atctgatatg caggatatct gatatacaat ttccaaaggg 2640
cttacaaccc atagtctgag aacagcttaa ctcaaaacac tataaacatg gaattatcaa 2700
agtgcataat tttctctttt ggttgtttgt ggatttttcc tatgttttac ttaataaaaa 2760
taatatttac tcttaaatca tgttttatct ttctc 2795

```

&lt;210&gt; 71

&lt;211&gt; 2554

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 71

```

aaaaagggtg tctctaatac ttgtatacag aattctggac aatgaacctt gcataattaa 60
cagattggaa cacacagaaa gtaaggcttc aaagaatagt attaaaacat taggttttat 120
gaagtggagt cattctattg ttcaagacc ttgcattgaa taatgttgga catggctcag 180

```

WO 2005/005597

PCT/US2003/027106

aatTTTTatga tGtagaagaa ttcaaatgcc aaatgtgcat ttgatctttt aagagggTga	240
atagtaagtt gttattgtga ttgcctgggc cctttaagaa atgagtgttt ggtaagtTta	300
tgtgtaacac ttgccatgat tttggttatg aataggtcgc aaagatgttc ctctgtctgg	360
cagatggaag ggcagcaaga taggtggctg ggaggaaagc cggaggcgga gttgtgctag	420
aaagaacata gcaaatcaa cagatggagg atgatagatc agtgggcaa aagaggtgct	480
acaggagaac aggggaagct agtgaagaca tggatggata gacagccagg agtgggctaa	540
atgaaccagt aataaaagaa atagagcagt acagggggcc caaagttcaa gaacaaatag	600
ataaatatca aagacgacaa ctacaaaatt cctctgtatc tgagcttggg aaaatatctt	660
cctttaaaat gtcttttatt ataatctttc aaaaatgctt taaatgaaca aagatctcat	720
atacggaaaa tctttattgt aaactttaga gattcatact atggaggaaa tttattctgt	780
aaaaaaaa tcatggatgt aaagttaatc ttattcotta gttttgtgtt ttctgcaaat	840
ttggattttt gacagctttt attatgtaa tatgtcagg cctggctgga aaataatgct	900
gaggtatatg gtccacaggg atgagaagt tgatttctt caatagagta gtataaaaga	960
atggaaaatg gaaatacagc attatcetta caaaatgtcc tgttttctct gcttaccagg	1020
agtgacaata gctatgtgct cattaacctt aagtaagtaa atatgttgtt tgtcctgttt	1080
ttgccttcag cctcaacttc ccatataacc accatttttc ttaggaaata gtcttacatg	1140
aaaaccetta gacagttaag taacataacc aagttccctt tgattaataa ctgttactat	1200
agattaatat ataaatgaca ggctcactaa tatatgcaga aagagggttg gcttaatata	1260
ccattataa ctgaccttta aatacctgca tgggttgcaa agctaactcc attgccccca	1320
tatacatgaa tgtagcaoga gcacttttga tatataaaaa ctggagccaa tctctgaagc	1380
aaaggaaac tttatggaaa actccacagg cactatggca gacgtgatgg taggcactat	1440
ggcagacatg atggtaggca ctatggcaga catgatggta ggcatatgg caggcattat	1500
tgaagacaga cactatggta ggtcccccagg gtaataaaag gcagagaaac aatcagttca	1560
ctcagagtcc tgggagagag tcattgttct tcagtgctc aggtacaatt atgaaatgca	1620
atggtcttgt ctatcttgt gagtccttta cttaogtgtg cctgtgtgct tgtgtgtgtg	1680
gatatgtgag ggtgcaccca tgtgcatgtg tgtccctatg catgtgtgtg tgcatgtgtg	1740
tcgtgtgtg tgtgtgtgtc cgtgtgtgtg cctgtgagca cacatagggt tgtgaatgca	1800

WO 2005/005597

PCT/US2003/027106

```

ggcaccatg tgcaaataga agttagaagt taattcttag gagtagaatg ttccctttac 1860
catgagttcc agggggtgaa cttggcttgt cttgcacaaa aaacactttt agtccttgag 1920
ccatcttggt gactaaaaga tgtgggacag aaggggccca aactcctatt ttctgcttct 1980
atgccttato aacacgtgcc accatgaatc ttttttagat taaggacctc actagattcc 2040
tcaactcagaa agtacttatt aggaacttcc ttgttcagtt gctctgtaga cagaagtatt 2100
tcaactgtttt cattgacaaa atgggtcaac tgaaatggga aaaaagcaa agaaaattta 2160
ctagacaact gcagctctca gaaagacata gagctctcag catagtgtact atacaattgc 2220
tgtgactacc attagtaatc agccaagaaa gcttttttca atatgaagat taaaagggtg 2280
gtaagagaga ttattcatta tagttcatga attacaatt cacacttcag agccatgtat 2340
tcaatgaaca caacttgcaa gtgcaatgg catgttctgg gctcagcact aagatactac 2400
aggttctctc ctatagccat gtaactcttc taaattcctt tgacagtttt gagacacctt 2460
caactgacca tgtatgaatc taccatgat attctgcate cttttaactc aaaggtttac 2520
ctttctttca ttaaaccaac tgtccccccc cccc 2554

```

<210> 72

<211> 3154

<212> DNA

<213> *Mus musculus*

<400> 72

```

ttgtctcagc ggaatggact tctcttaata taaaggtttc cagaatactc tgtcagaatg 60
aaggacacat ttccaataga gctgagtatt actcagtttt aactaacagc cctagacgtg 120
ggatagcagc tgctcggatg cgcagaagct gaataggatg aataagagaa acgcctttgt 180
aatatattct cctccaggtt ctctctgcaa ggaatcggga tcaatcctct tgtttctgta 240
acctccgcgc tcactaccga ggagacctgc acagattcac tgtcttgtgg aatctccatg 300
ggcaatcgca cttcagttct ttgaaaacat gagttatagt ggtatttggg gcttgcttat 360
toggttgttt gttattttat ttattttatt attttattat ttattttatt attttattat 420
ttattttatg tactccaggg agatgaagca attggaaagg attcattcct taaccagctt 480
ccattgccag agataaacct caagagtttt aaccacgacg gttaccctca tcttgaaaag 540
gtcttgccca atgcataatc tgattttatg gtttaagcac acagtccttg aaggtttgta 600
aacaggagca caatacactg gaatcctgca tctctgagta taagtctggg gtatgtgcgc 660

```

WO 2005/005597

PCT/US2003/027106

ttgcatattc ttatcccttg tgaagagga aataattaga aaatgagagt aaagagaaaa	720
aaaaactttc tttaaaaatg cctgtattgc tctttgggaa attatttagg ttgtctccaa	780
catgaaacat ccatgtgttt aatatatgac cttgaaaggc atgaaggaga gaataaatgt	840
aaacttcaaa tttctgccat cagaaaccaa aggcctttggg gtatttactt ctagccacaa	900
tttatctgca tacttttaaa atacacttat gctgtggtct tcaatattgg tggttttttt	960
aatttattaa atcaaaatca tttttaaatg cttctagatt gtctatcaa aactggggag	1020
gggcagggca ctcacaatga cagatcgggt aagctacaaa atcacttggc aatacagaaa	1080
ggctgacact tcagggtcga gcagagccac aaatgggaatg cgtctattgg tacttcttcc	1140
ctttttaggg tcaattaaat tctgcaggta taaatggctt atgcaggtag tttgttctga	1200
gcagaggcta agagagacac ccaagaatca tgtatcatga attgtctaa gtcagaatgga	1260
aggactagaa agcagcaacg tgttgggaca aacagaaaaa tacttgactg ggtatagtga	1320
tgggtgtccc ttcagtggta cttctcttgg acacctcga aggggttcaa acaggaagga	1380
cccaattctc cggaagaagt gttttgctg gggatgttta tctcagaacc tgagtctgt	1440
acagtctctg atctcogtta cctgagccag gcacaaactt ggggaaatc ctgtagtgt	1500
cttgagggtg gtgctctgc tttgtctat gccgaagag agatagttag accatagcaa	1560
gccaaagttt atttggaa ga cggtagtga aaacagtttg taatctgaac tgatgaagca	1620
ttatggotgc acaataaact aaaaatatag ggctagaaa atcagtacca tggctctcag	1680
ctagggttac tcacatgaca ttatttaatg atgagaagct gtgtattcca caggcatagg	1740
taggcaatat aattagaaga atgctttgcc agcagataca ctaggagtga actaatttat	1800
gatttttttt taagtacta ggacccttaa tttatctacc aggcacatcag tgaggtaaaa	1860
ataaaaaaa taataataat aaattttaaa ataagcattg caaatgcagt gccattgaag	1920
tactaaacag gaacttaaaa agcaacagaa caatttatgg ctaatgaagt agattaattg	1980
actaattggt gtttccatgt gtaattgttc ctgcaattat gattcacttg ccgctttcta	2040
tactgctatt cttaaacat atcctgacat ggagtggagg tagaagacat tggcagtttg	2100
ggagatctat tgagcaaaag atttttaoct taaagtgaga aggcaggaca tcaaaagaca	2160
cctgaogaga gctgaggaaa ctgtactcag catcatctcc tcgactttga ccaacctgat	2220
ggactttcat cttctaatgg gcaattatct aatctataaa atgacagggt atsggtttcag	2280

WO 2005/005597

PCT/US2003/027106

```

ccttaaaaca ggattagcca gtccaaatca caactgccg tgcctttaac gttttaagga 2340
gaaatgatgt attgatcatg cagagattc tattttcatt ccagacaaat tcaccttcca 2400
tgcaaataga cgcctggcgg ctgttccagg gtgctgtgta ggtaaaatac tgtgggggac 2460
actgtttccc taagaattac aacaacattt gaaaaacaaa acatgttgct ttccccagga 2520
atgtaaatct cagactgtgc tcaagtctga agagaaatat gatgggcca ggaaaaaata 2580
actctaaaaa taagattcaa acctaaacga tgtgcacagt aactagactt actcaaaaca 2640
cactctagaa atacattcct ttttattttt taactgaaaa taattttttg tacagtatat 2700
tttgatcctc atttttcctc cctcatctcc tccaagatcc tccccctacc tectaaacctg 2760
tccaaatcca cacctttccc tctgtcttta ttgatggctt gtttgatttc atgatgccaa 2820
agatttaatt gtgtgcttgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt 2880
gtgtgtgtgt gtgtgtgtgt agactatgcc acatgtgcc agatgcccat ggaggttgga 2940
agaagacatc ttctgtaac tggagttgtg ggtgccagca acttaagtc cttggaagaa 3000
tataccatgg gcccttaact ctaaaatgta atgttttagt tatttgagaa gttcatgcaa 3060
tgtattttga ccacattcag gccccactcc ttctctaact ctctctagac caattctcaa 3120
ctgcaogtta cttcaatat catgttctct tttt 3154

```

<210> 73  
<211> 1616  
<212> DNA  
<213> Mus musculus

```

<400> 73
tttctagtaa taatagtcca tctcaatca aatgttgct tagacttctt ggaagtcatt 60
ggtattttgt caaacaaaaa cagagagcca cactgtgcta ggtggccctg gaggatatga 120
agacatacga tggccctggc accactcttt ctgccacca agtgctctt tcttgctatt 180
aacagaatct aaacaggcaa ggagaactac tggaaaattt accatagaca ggtgaagggt 240
ttcatacaaa tctgttatgt agcagatggt ttatgtctaa ataagttctt ctaatgtatt 300
tgcatttttg aaaataggct acaaagtaac ttaatgtgat aactggattt tttataaagc 360
aaaaataaat tatgttgcaa atacacaaag acaattatgt atgttactag caagtcttat 420
tttgtacaaa ttacagaata cccattttta aaaaaacata cacatgacct ttgatggtag 480

```

WO 2005/005597

PCT/US2003/027106

atctctatgc tggcaaatat attctgata caaaggcact ttgaaaaccc aatatggttt	540
ggtttgtaag ttgcaaggt acaactatt tctacaaca tatgattaca ctgaagaagc	600
tcaacaactg tgacattaca tagaaaacag acttcttttt gtaaaaacaa cactggtttt	660
atgggaataa aagcagtgtt ttccagcagc tttagtgaag acattcagaa ggttgaaggc	720
ctccagtcgt aatttctcac tggctgggtg ggatgataag gatgggttga gtgtgatcag	780
caagaaccct cagcggggaa agataaccca ataccctaga aggaaccagc aaccctcagc	840
agtcagaatg gcttgaaggg aaagcacaca ggcagcagtc tgggcaggat ccgctgtga	900
caccgctcga acacgcggct gactctacct gcgtccttgg tgcttctgag ttgtagtggc	960
cgtgtctctg tttcagagca ctgggtagta caatgctttg gactgcacag tactgggaaa	1020
gtttggtcct caatcagttt ccttcctttg actacattgc cgcgaagtca atctgtacat	1080
aaagctgtct cactccagcc tggaaagtta gaaagaaaa ttacaacatc aaacctgaaa	1140
acctgaaaca gatgaacatt ctagaaaagt ggtaggaaag caaacaacac ctcatattgtc	1200
tttaaaaatg gaattatttt tgtcttttgc ttctaagaaa ctatccattt tcatgtgaag	1260
togtcaaac actacaggaa aaaaaaatgt gtgtcattag ccacatggcc tgcgtatgag	1320
cccttagatg ggtttattta tgtgccgcct ctgttagagg acacgacagt gctggattag	1380
gcagccacc attcaacca gctcaccagc ggctatatct tcccatggct tttaaaaatc	1440
acaagtggca actgcttact tattttacac tccgactcct tcagttcttg ccatgagcta	1500
gctactcaag ggcactactg tctaaattgc accctatttc ttctgtatta tcaattttat	1560
tctctcaact aggtcatttt tattagtgat caaacacact ataatttctt tcactg	1616

<210> 74

<211> 447

<212> DNA

<213> Mus musculus

<400> 74

taatgtggca caacgtgggg ctgaccctgc tgggttctgt ggccacgctg ctgatcgtcc	60
tggtgtgat ggtgtcggtt tggtattttg tatggcatct atttttatct aaattcaagt	120
ttcttcggga gcttgtggga gacacaggat cccaggaagg agataatgag cagccttcag	180
ggtctgaac agaagaagac ccttcggctt caccacagaa gatcagatct gctgcgcaga	240
gaagggccacc tgttgacgcc ggccactgag cagacaaagc agtgtcttag agtgtgggcc	300

WO 2005/005597

PCT/US2003/027106

aaggcagtcga cgagcctctg tccttagtgg cgacctaget ttgaaagtta ctaagtgcacc	360
gagggaacatt tgcaattgga tttatatcca gttttaaaaa aaaaagattt acacgtaagc	420
catatagaaa taaagggaaat ttaaacc	447

<210> 75  
 <211> 2706  
 <212> DNA  
 <213> Mus musculus

<400> 75 ggactgcctg caaagactga catttattta ctttcattggg acattctacc ctagtctact	60
tctcttcttt gttacatgcc tggctgggag acattatagt tggttactta aaaaaaaaaa	120
aaaaaaaaaa aaaaggagaa actggacctc tatgggctag cctgaggatc aatcagttgc	180
tattagtcca ctggagaaac gaattcaaac tttttaagag tagacctttt taatatccat	240
aatgc aaatc tgagaaatgct tataggatac taagctggca aatctgtctg aagtgttggc	300
ccatttctctg taactctata ctgtgtgtta gtttagcact tagtaggtac ttcacgaatg	360
ttttacctcc tgaggtcaca gtaatttgtc tgcattccagg ttcttagtgg aaatgcctac	420
cacattttgt acctagctag ctacttccac aggagaccag atttgtgtgc agtttatgtg	480
aaatacttaa ctcaggctcc aaatgttcca agtgtgtgtt agcttcttgc acagctccct	540
gttttcccta agaccacaac ttccaagat gggcctgata ggagaacaaa aaggcaggaa	600
ccctactttt gcctattaat gtggctaagt gagtttgtga ccagtacaga gtacatgcag	660
tccacacttt ggacaaggat aggtcaaatg ttagctccct ccccttaag aaaaagaaag	720
cattgtgggg ggtgcatttt gaaattttga cccatatact ttggaggcct aggagagctc	780
actgtgtcca gagaatttta gtcccaagg cctataattg ttgaaaagct agggaaactg	840
gcactatttg ggtaggagct gataccctgc cttttcaggt tccaggcag gcctctagta	900
tcctgtcctt gctcaggagt tatctttacc cctgaaatca aatactacac atagaccct	960
gtaaaaatgc ttccctgtaa gcttcacoga gcttgctaag taaacatccg cccatgcttc	1020
tggaacagaa ttcatttctg ctctctggtc atctctgtt tttctgttct cagtccccca	1080
ccgaatcatt ttaatggaag aaagacctag aattagttag aggcacctaa gatgattgct	1140
ttaattcttag taaatttctg aggaggaaga aaagttttcc tacagagtgt caccatactt	1200

WO 2005/005597

PCT/US2003/027106

tgcaagtcac cactgctgctc atggccattt ctctgtgaag actttagcac agtcttgctg	1260
tgttgacagac cacagtgggc tcaactcctca agttctatgg ctatgtttgt ccctacttta	1320
ttcccatgaa tctcttgctt gtttctcatg atttacctct tgtcaacttct acctaccatg	1380
acattcctat tgccatggca ctgagtagcc acatcattca ccaagttcat gagaatttga	1440
gctcactcta tgctgatcct acttccttct agttccccc cctgaaagag aaggctcctt	1500
ggcagagctc ttgttttatt tgatcctggg ctcatgggta aatctggaat gctctgacat	1560
gaacttaggc atgttttttg ttgttgtttt tgtttgtccc cctcccccgt gagaaggaaa	1620
ctggaaaatg gagatctgaa taagcagagg accattctgg gggccttgcc ttaagtgaca	1680
ttaaagccat atgcctttgc tcatcagacc agtaggtgac ttctttattg gcatacgcta	1740
ccctgcagcc cagaaggtgt aaatttgaa cactttcccc tcctgggat cctggcacia	1800
atgccctggg cttcttttaa aaccaggga taccagggtt tcttcagggt ggctcttctc	1860
tctgatggct gaaatattag ccagggtggt tgtgtaagg ctgtatagga tagttgggtat	1920
agaagagggt gttgcctgac ctcttggtca tctttctgaa agttgcaaga tgcattttat	1980
gaatcagctt attgctcag gacccaaaca catctaaaac atctagctag aggctgggtg	2040
agaaaacatt tatatatata ataagtata tatataatg ttggaacatg agccttggtg	2100
aatgtgtctg gttatgtagg gttoattggg ttagtatctg agctattctt tgtagcattg	2160
tcaggaaaagg ggatgttaga agctgtgctt tgctgctaag agttgtcact accotaaagt	2220
aaactgtacc tggctctgaa gcacagtggt aactttcttc ataagagttt ccagggtatgt	2280
ggatgtgtta aagtattgct caaggactgg gggttcatct ggttaccat cctaggggaag	2340
aaacagggtat tggctatgtt aggtctaggc ttggccatca ttctgttgtc ttttttgttg	2400
tcagaaggat cttgggaaga aatgactcag caacaaatct tagatgtgtg gccttctgct	2460
ctttggggaa gtaattgaac ataccctaact agattctaaa attttaacaa ctgaatgaat	2520
agacgtacat tactctggat ttcttcaggc tgctgtttgg ttattctttt aaaaacctg	2580
atctgataga aggatctcat ttgtggagtt agcaaaaaaa atgttttaat tatgtctttt	2640
agccttagga aattcaggat ttaaaagtcc tgatttcatg ccccaaaaaa aaacaaacaa	2700
acaagc	2706



WO 2005/005597

PCT/US2003/027106

<210> 76  
 <211> 1902  
 <212> DNA  
 <213> Mus musculus

<400> 76  
 gagacatcog tgggagcact gacagctttc acaccaaaca ctaaccagga gtcagctctg 60  
 ggtagagctg cccacgaagg aagagtgcct aagtcagcog tgctcatctt gaacctcaog 120  
 gcaggggaga oggaagcctg aagccccc tcctgtaga ttacttccc accagggaac 180  
 ttaccaatat ttctccaac ttcataaca aggaaggtga cggcttcgt gttactgtaa 240  
 gacagagaaa aacgtccact ggactctgct acacaaggca aggcacccc aggtctggaa 300  
 ggagcatcct cagggatttg tggtcctagt aggaagggcc tgaggactct tctgagagaa 360  
 caggagccaa tgaagagac cagcctccag aagcagagag gggaagggag aggcaggag 420  
 gtagtcagtc cttgggaaa atcagcccca ggtgctctgc cacagggcat cagaagtggg 480  
 cttcaggggg ttoggtcagg gtgacaagtg gagcgagcac cctgctgtga gcaccggctt 540  
 ctgcatcaag gaggaatgtg tatgactctg tgtgggttat aacaatacaa gtgtataatt 600  
 atcogatgat gattataggt atcctggatt tggatccagg atctaccctt gactagcttg 660  
 tgtctttgga catgcctttg gcctttgatt tctcattagt atcagaagga attgggtcag 720  
 acacttggtt agggctgata ctctgggggt ctttgtgcca accccaggaa ggaagctccc 780  
 aaggactcog gctgctactc cttgtgcctg ggaatgacag ctacgtatca gccccctgat 840  
 gcatttgccc acacogtttc ttgcttcctt aggaacctctg cacatgcagg gttctgtgoc 900  
 cggaaagcctt gtttgctcct caggttacag taggcaccto agtgaatttc atgttatata 960  
 agacaatata gtgtttaact tgactcagct acttaattta tgtctgtctc ttttctcatg 1020  
 gcatgagcct gtaaaggcca gaacctttgt tgttgttgtt gttgtttttg agacagggtt 1080  
 tctctgtata gccctggctg tcctacagct cactttgtag accaggcttg ccttgaactc 1140  
 agaaatccgc ctgcctttgc ctcccaagtg ctgggattaa aggcattgac caccaacccc 1200  
 cagctgggtt ttttttttta aatatttatt tctattcttt tgtttgtctg tttgtttgtt 1260  
 tcttctctct tctctgtctt ccttttggtt ctttctcttt ttttctcttt tcttctcttc 1320  
 tcttttcttt ttctctcttt tcttttcttc ctctctcttt ttcttctctc cttctctctc 1380  
 tcttctcttt ctttctcttt ttcttctctt ctttctcttt ttcttctctt ctttctcttc 1440

WO 2005/005597

PCT/US2003/027106

```

ttctttcttc ccttctttct ttcttatttt ttttgacaca tagtttctct atttaacagc 1500
cctggctgtc caggaacttg ctttttagac caggetggcc tgaaactcag aaactctgct 1560
gcctctgcct tcccaagtgc tgggaaggcg tgcgccacca cagctggtta tttatgttta 1620
gttacgagtt gggggtggtg tacatgcaca tgtgtgtggg tgtctgtgga ggcagattg 1680
ctgtgtaccg tggagctgga gtcacagggt gtcatgggct gcctgactag ggcagctggg 1740
aaccgaactc caatcctctg caacagtggg cagtgtctct aaccactggg ctgtctctcc 1800
agccccctcg ttaaggcctt toattgccat tttagcatc catgcaccgt ctgactctaca 1860
gtagctattt attaatatat attaaaatca gtaatgaatg gt 1902

```

&lt;210&gt; 77

&lt;211&gt; 1086

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 77

```

ggacagtaga ttccgagag gaaaggagaa gagaagatag ggatggaagc agagaagaa 60
agggttaggg agagaactgc gaagggatgg caggggggtgg tcacaaaag agaaagggag 120
aagagatcag gctaacttta cccaatcgat ccagcgatca ggtgacgtt tatgcggtat 180
caggacacga aaatggctcg acaatgcaat ccacaacaaa gctatttctt tctctagtct 240
agcttggtaa ctgctggaat caaatgcaag gcagacatgg cacagacggc cactcgtgca 300
cccctctac cccaccccca gtggaccagg gacagtcttc ggactgccct aacacttagc 360
ttctttagtc atggtcttta gcgcaggggc tcagtactga aagcaattgc cttaaacaca 420
ggctgcata ttttaacagg aagtgggacc taggaaggct gctgcgcct aggtaaccca 480
tcacagcct cttggtcatc ttgctaacc tccaaagcat agcgcctcg aaaactctga 540
gtgactacga ccttcaacca ttcacctccc agccctgtc tatgcaaaaa aaactcgtga 600
ggattagatc aatgcaattg gaccggctct gctggtttat ttgggtgtg tgttaagtcg 660
attttctac tatgcctgga tcagtttctg caagggaaag gattccaagg aagtctagt 720
gaaatgcact gatggaatac tattaactct aatgataaca ttcccagtc aggtaaacct 780
tgaaaagaac tgtgagtggg aagatcctgc aggatttccg aagcgtgct ctctggaatt 840
ctcattggat catcccccag agcctaaatc agtgctgctg ctctctgaag atgactacag 900
cctagctcac tagttgtcta ctctgttta caacacatcc ttctactct ctttgagat 960

```

WO 2005/005597

PCT/US2003/027106

ctgtttgtct tattcatcct gttctcttgg gttaccacgc ttctcactt tgtgggtact 1020  
tccagtttgg tacatttgtt tgcctgagga ttatcataag aaaggttccc actgttaacc 1080  
attctc 1086

<210> 78

<211> 3701

<212> DNA

<213> Mus musculus

<400> 78

gttctcgtct gctgaggtat gactctgagg tatgactcca gccacttggt ttccatttct 60  
tgcaatagtg tgatgattta gtaaagcacc atagaagaaa atgtattcac tccctttaag 120  
ttaggcaagt tgaaatttta ttaaattatc tatcttatta taaattacta aaattattctg 180  
ctaaaatatt ggctttgaaa gatattactg taatacgttg ctcaaaactc caaggttatt 240  
gggaaattag aatattctaa tgggagattg tgtcactctt tattcctttt atgtctgtat 300  
cttactttct tctgctgttg gaataagatt ttttttctt gccctgtcat ttcatatata 360  
gattatcata aataaattgg accatttaat atttcttttc ctaagaaaag attgaaccac 420  
ttaactcact ggtaatttgt tataataaga aatgaactca ttttaaatat attcttttta 480  
aaatccaagc actctcttcg aaacaattta tctctggcta tcgttacaca ggacttttct 540  
ccagccatgc tgcgccacc atgacttcat catgacttca tcatgacttc atcatgactt 600  
ctcttgcaaa agatctccat ggctaggctt attgcccgct tggctttccc tcatccaagg 660  
aaaagggtga aggggttaag cgccttatac caaatatagg gccctctgcc cagccagctg 720  
acggcaatct accctaattg cactgtgtct ctgggaggag ccagaagtga gtcacccggg 780  
aagaatgagg gggaaagctc tgcctcacc cccccccgc catccatgct gggttcagac 840  
cctctagtgt ggettttta tggctcacc agttcctccc cattatcact tactgattac 900  
tctaattgt ttagactcat tgggtcccc agtgaactct ggtgttattg ttctgtggtt 960  
tgtcatgggg acttaggagg aaggagctct cgcgcacaca cgtgcactcg cgcgcgcga 1020  
cacacacaca cacacacaca cacacacaca cacacacaca cttagagatg actctcaca 1080  
ctgctatgta gttcttagaa attcttatgt ctgtgtgaaa ggcttcttct aacagacac 1140  
attgctgatg ctttacagtt tcactgggcc cttgcctttt taatggcttc tctttactca 1200

WO 2005/005597

PCT/US2003/027106

tctgcctcac agtgattgat gtcattaaat taccacgcag agtaatcata aatattgtat	1260
tatgatattgt atttgaaaat tgagtcattg cagagaggag aggaactatt gcacaatttc	1320
ttcatattta ctattttaca taaatatcac ttaatggaaa aatagtgca agatgtctgt	1380
actaaattgc cgtggtgaag ctgagcttag gaaagaagt gcattataaa tattatcaaa	1440
acaatgtatt atcagacttt actttacaca ggggaatcta ttttgggagt agaagcatt	1500
acctataagc cttgttataa coaagtttcc cgttatcatt agagctccta aaatacactt	1560
gcagtcctga ctataaaatg tcattttgta caaacctta atcaattatt ttgctttaag	1620
ggttttttat ttttgttggt ggtgatggca gtggcttttg ttttgtttta ttttttcatt	1680
accagcaaat ggcaccgcat tactggtaga aataaagaat gggcgcttga taactacagc	1740
aatatgcatt gtttcttttt ctttcttttt tttacagaa caaaaaaaga aatataagag	1800
tttctattcc tcttttgcac acacatatta atacacacac atgcaogtac tactagggat	1860
tgatcggggg gcctccccc tgctaaattg ctttgcctat cttacctag ctcagcctta	1920
tttttaagtt ttatttggag aagaagtgtc cttagctcac ctaggctgtc ttgactctct	1980
atggagcaca gacatgcctt gaagtttgat ccttctatct cagcctccag tccagatgta	2040
gatatagggt tgtgtacta tgccctgttg tctacaaagt catgccttg tgacattaag	2100
taatgttaat gaattggaat tagcttcatt cagggttcctg gggcgggggg aagtaactcag	2160
tcccacaaac tttctccacc tcagatgcca ggtgcatgtt tctagtcttc aggttgccag	2220
cactctctctg tgcctctgtg gccctctgtg cctctgtgc cctctgtgcc ctggctacaa	2280
agctaaagca ttctactctt cctactacgg ggggtgggca tttgtaggaa caactcttaa	2340
ggaactccaa aacacttact tgctgttacc aatgaatgtt attgtatta ttgattatca	2400
gaaagagcca aatgaatgat gcttaaagta aagtgttggg gaggagacct gacctattca	2460
gggctttgtt ccagttgcga agtatcctcc agggaagccc actcagatgc aggttcaaag	2520
caatagccag tctttattag tcagccagta gctgcagtgg gtgtccaaga ccttggtgca	2580
gtccccagcc tttctogagg tgagctttta agcacagagt ccacaccctg gattggcaca	2640
ccacggttgc tgagaacagt tagcaggaag cagaactaca gaagccaaaa agcgaggctc	2700
ctatatttag ggactttccc ggaattatgg actttgatgg atttgacctt ggttgtagat	2760
ttggccagtg ttactgtcac atgaagagtt taaagcccat acaatgcttc tatcctgctg	2820

WO 2005/005597

PCT/US2003/027106

```

tcagctatgc taaggctctgg gggcccttaa caatgcctat ttggacaca ctcttgttcc 2880
cacacctcag tgtgtatata tcagtgtgtg tatatcagtg tgtatatatc agtgtgtata 2940
tatcagtggt tatatatcag tgtgtgtata tcagtgtgta tatatcagtg tgtatatatc 3000
agtgtgtata tatcagtggt tatatatcag tgtgtatata tcagtgtgta tatatcagtg 3060
tgtgtatatc agtgtgtata tatcagtggt tgtatatcag cctaaaggct ctctgaacct 3120
tcttgcttag gaggggatgc atgtgttctc ctaactaata tatatattta gcaatgaaa 3180
tattggattt cactttgaca ttttcataca cacatattaa tatactttgg tcataccac 3240
ctctatcacc ctacattctt ctccactccc atggcttctt tttcccttc caaagacttc 3300
ctcctctgct tctcttctt atgaactttt aaatcaata tgtgtatata ccatgtgtat 3360
atgtgtttgt gtgtatgcat gtacatgtgt gtgcgtgtac atgtgtgtgt gagtgtttt 3420
gtgtacagga gtactggggg agaggaaaag gcagagtgag catgagtaca gcaggaaacc 3480
agggatacac tatagccctc tgcaggctat aatactcatg tggctctgtg cctatggtaa 3540
gctgagctga catagagctc tgcattcctt agcccaactt cagttttctc agtcagttgt 3600
tactctatag ttaactaaca agctaccatt gcaagaaagt gacaaacttc caccacatct 3660
ctccatcagt tttaacaatt cctacactt ataattgttc c 3701

```

```

<210> 79
<211> 2346
<212> DNA
<213> Mus musculus

```

```

<220>
<221> modified_base
<222> (2281)..(2281)
<223> a, c, t, g, unknown or other

```

```

<400> 79
gataggaaaa ttttggaggg taaacgagga aagacaataa catttgaaat gtaaaataag 60
aaaaatatcta ataaaaaatt aactaaaaat ataggtaata aatataacctg ataaatatgt 120
gtaactaatg ctaacctagc ttttcttcaa tattcaagga gaataatgat ttgtaaaaaa 180
cgtagaatta ctaaaaagga aatgtaccat atataaagtg ctcaaaaatg cctacaatta 240
tagaaaatgc aagaatatta gactaaaata cataacaaaa ggagaaacac agagtatttg 300
agagaaagtg tataaatgag caaaatgtaa ggaacacacc tttattcttc ttgtaagtgt 360

```

WO 2005/005597

PCT/US2003/027106

ggacatcttt ggagttcttc	aaaaagaaca	aaatgaaga	gtcagtagaa	gaaaacatgt	420	
cagaaaaaaa	aaagaaaaga	aaacatgtca	gaatgaatat	tatataaaca	atgctgaata	480
agcaagtact	tagagaaaaag	gaagcctttt	tacttttttg	gatggaaatt	aaattgggta	540
ataactcacc	agagaaaagt	tatggagttt	ttcaaaatca	tgaagaattt	gtctgtcatg	600
caatattcag	cggttccact	taggagtaca	tgttatcatg	tgcttaaaact	tttctaagac	660
agcaaatggt	aagattgttc	agttatttaa	gtgtgtgtaa	gtacgaaggc	ttgtgtctag	720
ctggcaagaa	ttaaggtagc	atgacatggt	tcacaactat	aatcctaaca	ctataaatga	780
ggaaccaggg	agattcctgg	agctggctga	cagctagtct	tcocaaatca	atgaacacct	840
gtctaaaaaa	tcacggtgga	gagctatgca	ggaaaaacac	gatatagaca	tggagggttca	900
acaagcttgt	gcacacacct	gcaagaacct	acacatgtgc	acacgaaagg	caaacctgaa	960
gccatgacac	acacacacac	acacacacac	acacacacac	acaccacaca	cgattctgta	1020
agacaactaa	ttataaaagt	cttaataata	aggtttgcat	ttaataata	ttttcttcaa	1080
ggaaaactaag	aggaaaaaga	gacatttaat	gtaaagtgga	aaatcagaga	cactatttat	1140
gtacaatat	tactataaat	aagtatatatt	agttaaagtc	aattggctct	ttatacattc	1200
tgacttcgag	gcacatatgg	actcctgtgg	aagtaatttt	aaatcagaga	taacactaac	1260
aatatacttg	agccatcttt	tattttcact	gcaaaacttt	agtactgttt	tattttactaa	1320
gagtttggat	accatatctt	aactgataag	ttgaaaaggg	ggaagatagc	tcagtagcaa	1380
gaattttttc	tgatacaaa	aaatgtgac	ttcaaataga	agtattagtg	gggtgtgtgt	1440
gtgtgtccat	gtgtgtgtgt	gtgttttgta	atggtgtatg	tgtacactgt	gtatttatat	1500
gtatgtgtgt	gtgatatgta	tgtatggctt	atgtatatgt	gtatatctat	tctgtgtgtg	1560
gtgtgtatat	gttgtaata	tgtatatgta	ttatgtattt	atgtatgtgt	atgtatgtat	1620
gcatatgtat	ggttatatgt	gtatatatat	atatgtgtgt	gtccagggtc	tattctgcct	1680
tttttaattc	tctgggttcc	tccttttatg	agaggctttt	agctatagtt	aacttttttg	1740
aaagcagttc	ctgataaaat	aagagatttt	cactttctgt	tcaagttatc	ctcatacatg	1800
ataatgttaa	aataatgttt	ctgaatat	gtccaataaat	gtatctaata	actactttta	1860
aataatgcc	tcctagtaat	ttccttatat	acaagatat	gtatagttta	gcaattatga	1920
aagtgtcaaa	gtatttctat	cccataaatg	ttacttagaa	atgtcaataa	ctataccaag	1980

WO 2005/005597

PCT/US2003/027106

```

agatcaaaaa cattagacta aaacaaacca accacataat acaaaatatt taatttttaa 2040
gagaaagtgt gtaataacca acattttaaca aactccccctt tatctttctt tgaagttggt 2100
gcttctttgg aatcttctag agaaaaataa aaaataaatc acagtctaa gttcttttgt 2160
ttttttctaa aagaatatct tttactttac tttaaagggtt tttttttggg gggggaagcc 2220
agtttagagg tctctctaat cctaataaaa gtgttcctct tttttatata aaaatttaat 2280
nttttatatt taaactatag attatacatg attttgctaa ggagactgcc ccaaacata 2340
tcttcc 2346

```

&lt;210&gt; 80

&lt;211&gt; 3320

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 80

```

gggagacacc ggccttagcc gggacaagca ggggtgggtcc tctgtggcag gaagggtggc 60
tgggcttgct tcaggttcaa cgtagagatc gcagagagca tcgccactgt cgtatccct 120
ggggatgacc acctctctgc tgtgctgctc gttgctgatg ctctctctct ctgggccagg 180
ggtggtggag tcccagtagc cctcatgct gttaggaaaca ccttcttgat gctcctctc 240
cggatgtttg ggctcctcct tctgctggga ctcaatggga attctgtgga gcctcctgcg 300
cttgaccgag gacatgtcct tggctgcttc cccacacagg gtatcactgg aggtctcagg 360
ggccaacttg atgtcggaag cagtggctgc ctgcctgcg ccttcttgag ttcttctgcc 420
ttggtctcca gtctgggaca acatgtccca gaattccggg agatagggtg cgtccacctg 480
atccgggctg gccatctcct cccctcctcc ttggtaggac accacgctgg cgttcttttt 540
agagagaact ggcttgctcg gcccggggac atgcttgcca cagctggggc ctgcctcttc 600
ttctgggtct gcaataatat ctccaacagc tgtaagagag tcaaaagcttt tcagtgaagt 660
cacgtcagaa aacatcaaac aaatacagtc tgcgcacggg tctgagggtg gatcaacaga 720
ggaagcggtca gggacagcag acgcccggcc gctgccacct tcggagtcga caaggggggac 780
ggtctttatc ggaaagtcac ctgtcttgga cgcactctcg gccgctgga cctcacgggc 840
tcccagctcg agggctgcc cggcttctc ctgcgcgcga tgccccctgg cgtcctctcc 900
ccgggagcct tgatcgccag agccgggtgg gctcccggcc tcgaggcaga tcgcctcggg 960
ggcgctctcg gcggaacggg gcgcctgctc tccccctgcg ggctcacctg ctgcgtgtcg 1020

```

WO 2005/005597

PCT/US2003/027106

cgaggcggtcc	tggcccgggc	tgtccggggc	gogcgcggtc	cgggcgggct	cctccttgac	1080
gcactccagg	ctggcggtga	gogaaacggg	cagaaccagg	ttgcccgggc	ccgcccgcgc	1140
caaccgcttc	tcctcctcct	ccttgccgcg	cttgctcctc	oggtgccagc	gcattgctgt	1200
gaagatccct	ttcagccccc	tcttttggtt	gcgcgcagcc	ttgctcgctt	cgggcatggtc	1260
tccttgccgc	gtctccgata	gccggttctt	tttcagcagg	gagaagaagc	tgtgggactt	1320
ggccacccag	ctgctggcca	gggagccag	gccaggccgc	gagggtttgg	ggggtcgggg	1380
gatcgccggg	gccccgctgt	gatcgctccc	gccaggcggc	tcctccttct	tgtgcctcct	1440
cagcaccaac	acctcggtta	gtcgtctgtg	ggtcctgctt	ctcaccattc	cgttcggccc	1500
cgagctcttc	ccatcccttt	tgtttttgac	cccaaaaatg	ctgggcatgg	tgccccccga	1560
tttcttttct	ttgaataact	tgaaacgcgc	cttattgata	ttccccgacg	gcggctctgc	1620
ggggggcgct	tcgcggcgcc	actcacaatg	cgagtccatg	tctgcagcga	gggcccgggc	1680
ctgctcctgc	ctcccgagca	cccccgcgcg	cgccgcgcgc	ccgcgctcgc	tgacagccgc	1740
gcgcgcgcgc	cggtctctgc	cgtctccat	ggaaaacgag	tgggatacgc	cgctgtgtgc	1800
agccgtaggc	tcgcgccagg	ccactgtcac	ccgcgttcta	aatcaaacctg	agccggtctc	1860
gtgctgcgcg	tgtggctact	gcaactgcgg	cggtgaagc	gcacaaacgc	gactatctcc	1920
cctcctgcga	agggcttata	taatatcctg	ggtgccacat	aggtttttgt	gtagcaagag	1980
ccttcactgc	agcctcgagg	cgaagaaaa	aaatgaaatt	cataattatg	ggctttggat	2040
ccagtgctgt	tgattctcac	caactcaggt	tcttctcctc	ctagccacgc	ttttcctagg	2100
atcgcgcttt	caaaaaatga	cacatgcgtc	ccccatgtcc	acaaagaaca	atgccttttc	2160
ctttatcctc	tgttttgtag	ttcatgcagc	ctcctatctt	tctccggtcc	ttcacatagg	2220
tcttagcggtg	tgggtactaa	gcccaagagg	caccatgcca	atctgttcac	gcttgcgtct	2280
ggtccagtcg	cgaatgtagt	cctcttcagg	ttgatgctgt	attctgatca	tgttggtctg	2340
atttctgttt	acagaagcaa	cagccgtcag	tcaaatacca	attagcagct	ctcagcaacg	2400
aaagtgcac	agtcctcctg	ggttcgctgg	tcctttggga	gaccacaaag	cttttatccc	2460
ccacccccgt	gacatggggc	ttaagtccca	gaagccacca	attggtcaca	atagaactgag	2520
cacactgaga	acttaggttg	gagaattctg	atccctctgc	aggtgggtct	tagaggcctg	2580
ggctcagctc	tcctctttca	ttcaggggta	tggttaagta	acctctctct	gttgtgccca	2640



WO 2005/005597

PCT/US2003/027106

```
gcctaccctc gtetaagaac acccaaggac cccactcgct gtctttccca ataggacagg 2700
ggggaaaacc agacaggggt cagaggtcgt cctgtggtt gcttctgacc ccactgggtc 2760
agaggcaag ggaactgggt tccagagaac aacctgtgtg ggtaagggtt ctgtgttctg 2820
actttgaaga caactgctaa cattgtagct tttcctaacc aagggtctgc cagcaaaata 2880
gggaaggatt tggaaaagat tcatgtttta taactcttaa taacctatt ttaaaaaatat 2940
tgattatata tagtgattat ttgattgtat atactattta catacaaca ccagctcttc 3000
ctgcttctct tgaatttatt ttccacaagt tacttatatt ttgcagattc agagttactt 3060
atatactgta cttatactga actgcagatt cagttgttgg ccaaggcagc ctccaggggt 3120
cacagttaga ccatggagtt gagcagtcatt gttgctcttt ctcatctcaa tgaaaaaacg 3180
gtgtgaaact gagactggaa tcaaaaggacc tttctgtttt cagagttcaa accccaccag 3240
ctctttccac ctactaacag gactctttat ggacagaata tacaacaaca gacttttaaa 3300
aaaaaatgag ttttcttttc 3320
```

<210> 81

<211> 1573

<212> DNA

<213> Mus musculus

<400> 81

```
gtaggagaga aaaagaaca actatagtga agtgatcagt catttcattt tttttttttt 60
caagcaaggg ctgttttgaa agaactcaaa aaaaaataaa aataaaaaca atgtgaggtt 120
taatataatt ctgactctgt ccaacagaca gaaaattaga actctgagaa cttggaaaca 180
cacagtgtag ttctctgcct ttgggtttta taacttaatt ataagggtt agtctgatg 240
gcagcagtggt ttcaactttg ttctctatt tggctctatt gtttttttaa cttaaagaaa 300
ataaccoggg aacttgacat catatgcata gactgtgttt cttaacacac aaatggacat 360
actatacttg cgtatatata tgggtagac aggttttgc tccaacttca ttgtttatga 420
agtcataatt tgggttttac accatctccc ccccataagt tattacagaa aaatatcagt 480
ttagattgga caaagttctt cccctctca ttaaaaaaga caaatgaagg agaggggatac 540
attttaataa tttcctttct ccccttttgt taatatcca gtgcattttt tttaccttgt 600
ctacatggga aatggcttac tccccacaca atagaatatt ctggaagggt taggtaagaa 660
```

WO 2005/005597

PCT/US2003/027106

aacaaaacag aaaaggcaat ggctatactg aaattaacac cattaaaact gtgatcagtt	720
taaaaaatta aatagttatc agcacaaaaa ggcgttaaaa gggaaaacac ttttttatta	780
accttaaatg ttctggattt tatttccttg ttaggtatca gataaatggt atttcaaaca	840
attaaattct cactaccata caattatggt tcagcatcag attagcactg cactccgtag	900
ttaaggtttt agggaaaatg ctttatccag tattgtcttt acaaacatct gtgattgttt	960
cattttcaat gtttttaca gataaatggt gacttataat gggcatattt atttgctgtt	1020
atttcatttc ccccaatgaa tgtcacagga gatgccatag agctatttca gggtatatca	1080
cactgctgtg tcctgatgtg tggggactgg ccttcagtga agcaatccag agaagggcaa	1140
atagccaatg gtaaaaggag gaaatgaatg tgcagatacc aagtaggtaa ggtccgaagc	1200
tgggggtctc tcttgctctc ttaggcttac aaagatggac attaccactg aaccttacca	1260
tatgtatata tgtttaatat ctgtcttttg aaatgcagaa atagttaaaa tgtttctttg	1320
tctatttttc tttttctttt ttttaaatgc taccagggga aatatatttca tatcgtttta	1380
cgtaggcctg ctaaatgtat atttatttct ttggagcaaa aagggtctga aaactggttt	1440
tctgtagcct taaatgagta ggtagcaaga tctatatggg atgtcatttt tttgttcagt	1500
ttctttttta aaaaatgctt gttttgatac atttggttgt gcttggtggg aaaataaaa	1560
cgcagagatc ctt	1573

<210> 82

<211> 868

<212> DNA

<213> Mus musculus

<400> 82

taatgtttct cactagcagt ctgggcatat gctggtgttt catctctgcc caaataattc	60
acctcctaac ctatgtgtgt gtgtgtgcac atggatgtgt gtgectgagt gtgtgagtgt	120
gtgtgtgtgt gtgtgtgtgt gtgtgtgtgt gtgtgtttat gaacagtata ggttttaaaa	180
gaacagtatt ttacaaaagc catcactttt ataagagttc tgtaaggaa ggaagtactt	240
cttcgctcac tatagttaa aaaaaattct attttagagg aaaaaaaaaa aaaatatgag	300
ggctctgagc atgactttta taactagttt cagttttatc taataactta cttttaaaaa	360
atcaatatat atcaataatt ttcatgtatg ctgtgctttt tgagagacat gtttggtgtg	420
tcagtaaaag ataagagtat atggcctaag aatcaaaaag aaatgaaaaa ataaaataaa	480

WO 2005/005597

PCT/US2003/027106

```

aagagggaaa agaaaaatga aaaggggaaga aagaagatgg agcaaacaga aatttctatt      540
gtatttttagg aaaatgcacg attttcaagt attttaaata ctgagttaat attgttattt      600
ttttttaatt ccagcagtaa caaaatgggt taacctaaact ggcttgcgtaa gaaacgtgta      660
agtcttagat ttgaaagaat ttaacattca tagctctgga ttgaaatcaa aggtcatttt      720
ctgcaaaatt ccttccttag atcaggtcag tgctctgctc ccttcaaaat agaaggggca      780
agctagagtg gcagagcttg tggcttctat ctgacacttg ctttgggtaa acaggacctt      840
tcctcctgctg ctgcatgtat agcacttg                                     868

```

```

<210> 83
<211> 1888
<212> DNA
<213> Mus musculus

```

```

<400> 83
gagaggggaa cttgtggagg ctctggcagg aaagtgtggg ttctgtatac ccaaggctgt      60
gtgcctaggt gtacctttcc ctgggacttt gcctctctgg atcagggtgtg tgtctgaacg      120
tacatcttcc tgtccctctg tctctcgtcg gatctgcacg cttgcctctg caaacacacc      180
tctttgaagg tgttgggctg cctgtctctc tgtgtcccta tctctgagtg tcttgagtct      240
catttctcta ccagtctctc tgtgtatcac tgtctctttt caagactgca tgtccctttg      300
ccctcgggga caggctotcca tggggctogg atcgggtggt ctgtgogtct tgcattgtgc      360
totgcctttg tgtctatctc tctcccaagc tgtgtgtctc tctgtctctg tgtgggtcac      420
tgctctttta taactgtcca agatctctgt ttttgcaccc tctgcccgta ggggagcccc      480
ccttaacctga gttgagcccg gtgcgcgcgc gcgagagggt ccgggacaa cgggagctca      540
ggcccgactg aggtctccaga gcctgcgggc gggggggcgc gagaggcggg caggggcgac      600
gtccactccc cgggcccctc ccctgggccc gcagacctcc gccggcgcct ccgcgcgggg      660
cgcgacgggg ccggcctctg ccgcgggcgg tctgcggaga gccggcacct cctccccctg      720
gggcggcgcc tctcccgagg ccggggccgc tagctcgtct cctcgtctgc tctctcgtct      780
ggcagcactc gggcgccgcg ggcaggagcg tcgaggaggt cggctgggct cggctgcggt      840
tcggctgggc tcggctaagg cgggagggag tcggctaagg tcggctgagc tcggcgggca      900
gcaaaaaaca goggagagcc ccgcctcgtg agtgggcagc ggcctcgggc cctttggggg      960

```

WO 2005/005597

PCT/US2003/027106

```

aggagccatc tctgtgcgcg tgcgcgcgtt caattggctg tcggggccaa gttccgcgcg 1020
cattggttgt gctctggggt gggacacgac catcctggtg caggagagaa ggaggggagg 1080
gcttggaag ggtgagagga ggggtatata ggggccactt tgttttgatc catcccttga 1140
aaaggtgaag ggtcagccca cctttttgca gggatttctt gcatcttcca cacctggaat 1200
gcacccccac atgtgaagcg tccacccctc catatctgag agaagtctgt ttctattatc 1260
tgagaaagtc catgtgcctc cacacctgac cctctcacc tatcatcttt ctacatatcc 1320
ctctcccagt agagtgtaga gtacctcatg tccactttac agcgctgta gattgccctt 1380
agtctaata acagtgtgat ctctgggaat tcatgacctt tgttgcttt tactgatttc 1440
tcaccagtg ttggtcacag ggttggtgat ggcttgctgg agggaaactg agacacctga 1500
agaatggccc agctctggct gaactagatc cagacggcat ggatggcctg actctccatc 1560
ctaacagttc tgagaccaag gttagcttga caggagcagt caagtaggcc ttccctctc 1620
agacccttaa gtagcagggc tcacacatgc aaggagctac atttctggcc cttagtgat 1680
tcttaagtgt acttggtgtg ggttttatc acatattgtc catggacagt cagagacca 1740
tgccccaca tccagcctta acttccctca gaatactata ctacagcaa aatgcatact 1800
ggagtacag tgggtgtgtg tcctggttcc actttctaac tctcttaaac gaagctttct 1860
tctcaataaa actgtcatag taatagct 1888

```

&lt;210&gt; 84

&lt;211&gt; 3946

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 84

```

aaatagcacc aggcctttgt gatgatgtat aagaatacat gcctatctgt tatttaagaa 60
ggaa caattc tatagcttc actaagtagc actgagtcta ctatctagc cttaaaaaata 120
tatcataaac tcggagacct gatgccttaa gaaaccattg actttgttat taataggaca 180
caatgtttcc ctgtttttaa cattttattg tttatttgtg tacctgtttg tataataat 240
ttgtgtgagt ggtatggaac acatgtgcta tgacacacat tagcggtcag agaacacatg 300
taggagtgga ttctctcatt ttgatctttg attccaacaa ctgaacaatc ttatattagt 360
gtgattatta atgtgatgat aatattaata ctaataatag ctgttcatca ggcattaaac 420
ttttctact ctacacactg ttctcattgt tttcaatcct gtttattatt ccaacatctg 480

```

WO 2005/005597

PCT/US2003/027106

catgatacaa	gcagaataat	tctattctac	agaggagaaa	gctgcagctc	agaagcatga	540
aactcagcaa	tacaagtagc	tcctgtaata	agaagctggc	attcagctctc	aggactagtt	600
tcctgactat	ttttttttaa	agagttggta	cggtctttga	agccaccatt	gtctagcgca	660
agattatag	ttattgtttt	ttctttgaca	tattgactaa	tgcttctcag	tgatgttatt	720
ttttcttctc	ttggtttgct	tttgaagagg	aaatgctcaa	aaacagaaag	ggcgcgctc	780
gcacaaccta	tgtaatacag	attaatattc	aaagttccaa	gctgtacttg	tatacacatt	840
tagtcatgca	attaataaat	taatacttta	ctgattttct	tctctgtgct	aggcactgat	900
aaaataatga	tagaaatgct	aacgtgatct	agctcgggaa	agaaactttc	tgtaccccaa	960
tcaaactgat	caatctttaa	aaacaaatac	tttttcttat	cagcaccatg	attcatctta	1020
aaacagaggg	tctgctgaag	tttgtttgaa	cattgttaca	atagctttga	acattatgat	1080
agccagtttt	caaagtagtc	tgccagctag	tgtttaactt	taccagagg	gtctaataatc	1140
atacaataa	taaaactaat	ttaaaagaaa	acagtgttca	cctttaaaaa	tgtattttaa	1200
tactgagtaa	attaataaaa	aatgtatgaa	tgtcatctca	ttttactgta	ttcttgaaag	1260
aaagtgagtg	cctgaaccaa	atatttagca	gtgggaatta	taaaatcata	agacgattaa	1320
gttagctagt	cttagaattc	caatattgct	ttttaaatga	cttcaggata	taggaggtac	1380
taagggttatt	atctgttatt	tggaaatacag	tggaaattga	caactggata	ataaccaaac	1440
aaactgacac	aatgtaaaa	tacattatca	gtgtgtttaa	acaaaattgc	gccctaaagg	1500
agtcacatg	ccagctcaga	gctgcagtgt	aattatgctt	aactctgata	attaaaaatac	1560
aacggagatc	aacagaatca	ttttcattaa	gaaaattatt	aatgatgggt	gtatagcagt	1620
aattgatctc	agagcaccac	aggataacgt	gacgctggaa	accacaactg	tttaatgatc	1680
gtctgaggct	ttttgtgggt	atgttctgtt	aaaatgggaa	atacattttg	aggcatgagc	1740
agttttatt	gcctgctctg	agaatcagtg	attgggaaaa	tggtctgattt	agaaaaatcac	1800
agttttgatt	caagggtca	ttgtggagag	gtttgcaagg	tcaagacaag	cggccccacc	1860
aatgatggag	ttattgttaa	cagagttttc	tattgcaaat	agcagaatgg	cogcgtgttc	1920
agcaaatatt	ggactctctg	ctgtttccat	ttctttctgt	gcattgccag	gttttacaat	1980
tgtgtcaatg	gcttactagt	attgtgttga	cccaagtctg	cttacacatt	tacagttatt	2040
aatgtatgtc	atgtatgcaa	atctataact	gttttcatac	agatgtcatg	gtgggtttac	2100

WO 2005/005597

PCT/US2003/027106

tagtaataa	gcctgtaata	tatcattggt	acctaatga	gggagatgtg	ctaacatgtg	2160
gtagaaaaa	atattttaa	cccacttggg	tccatatatg	agtgaagctt	gtgtctcttg	2220
agggatagaa	actaagttag	actgttgcca	aatgataaga	actggggata	tatcagtggt	2280
atgtgtataa	aaatgagaaa	tgaaaagcag	ggtctttgga	gaggtgaatc	actatcatgt	2340
gaggatgta	gottgtcagt	caaacagatg	ataatcttga	aagctacccc	cagaagtatc	2400
tttgtcagct	aaactgaggg	acaactccta	agagtaaaat	tttttagaat	aagacatcct	2460
aaatagcttt	ttaaacaatc	tacagaatag	atgaagttgt	tgcttataaa	tgctagttga	2520
gaaaagcaga	aaatatgctt	ttgtatccac	tataattaga	gtaacattta	aaagcatatg	2580
cacaagaaac	agaggggaaat	aaaattgcac	gaaattgcaa	aagtatttct	gtaaggagaa	2640
atttgtggcc	attatttgtc	tctacttatg	ttacttattt	gagagagaag	ctaaactcca	2700
agaggcacta	gcaagtgact	tgtgcaaac	actggacttt	gaggcttgta	tectctctta	2760
taataaaact	tcttagagtt	tttttctcca	tagagtttaa	gaaaagtact	tacatatcca	2820
aatcctatgt	cttaactctgt	tctcagactc	attcattcat	tcactcattc	actcattcat	2880
tgcatccac	tgctggagat	gaaacccctg	tctccaagtc	tacacatggg	ctgggaacct	2940
gttgcccat	tgcatgat	cagcccttct	tttatgatcc	aaaccctaga	ataagaaatg	3000
tttaattcac	aaaatcctta	ttccacaaaa	attgatgttt	ttgcccctgc	ttatataa	3060
aaactttctt	aatacacata	tgaatgcctt	aaaagtattt	ttccttaaga	tagtttctta	3120
aaaaaatata	agtaatacaa	cacatgcata	ttctccaaat	tatgggtattg	gaatgaggat	3180
acaaattaat	ctaaaaacaag	ctttgggtta	acaaagtcac	tgaaaaccttt	attaatcaag	3240
tatacttaaa	catttaaaata	atgacttcag	tcagtagctc	ataagcaagc	cgagactcat	3300
gaaggggtgtg	aaagttgggt	ttgttttagt	ttgtttaaaa	ctaagccatc	agttctagga	3360
atgggtgagg	gcatttaaa	ggtttgaatc	tgtgagccta	gtggctcata	gogtgggag	3420
ctcacagagg	acagttttgt	aaggctaggg	aacttgcaaa	tgagaacogt	ga tggcgaa	3480
ttagtttccc	accattcact	tgactgatgc	cgagtctttg	attatcaogt	catggtagag	3540
ctgatcatcc	agcaacatcc	gtaatccaaa	tgagagtttg	tcagataact	gtgtcaaaaa	3600
caaacttgta	tccacattca	tttgaaaaact	atatcccaat	gggaaaaatg	tggttgtagcc	3660
acacacttct	agcaggtaat	aaaccagcct	ccttccctcta	ctgtttacct	gaattcggtt	3720

WO 2005/005597

PCT/US2003/027106

```

tccttattcg taggtcaact ggcttgtgtc acatggatcc atcattctaa acactccatc 3780
cacctcttac gcttctcttt tcatggcctt tatcagcttg acaatactgc tggccatttg 3840
ctgttctccc caacttactc ctggttggac ccagcagaca gatggttact atttgtgaaa 3900
tgctcggaat agcacctgtc tagttccttc tctcattcct gtgacc 3946

<210> 85
<211> 2805
<212> DNA
<213> Mus musculus

<400> 85
taacatatag aagaagatcc caaggatctc aaagtccttc agatgtcacc ctcttggtgg 60
cactgaaaag atgcattgca catcttctcg ggcaccttcc agaaataata gttttgagac 120
taggtccacg tgatatggag agcattcagt gtgtgatggt gagactgtgc gcattcttcc 180
gtctctctgt gttacagaca gttaatgtaa aaatggcctt ttattggaaa cacaaatatg 240
tattoacttc aagaatagga gcagaggggg gacaaagtgt ctctccggtt ctctgtttat 300
tgtgtgaaaa ctaaaacaaa caaacaaaag cggcaagtgc tgtaatttct caagtcaagc 360
catctctgtt gtgggcagggt tgtgcacttt ctttcttcaa ggagctgaag tatgctttgc 420
acacctttct ccaggagggt ggcatttaac tgtggggctg tcagggggct agaaaatgca 480
gctggatgtg gaactgccag gctggggcag ggcaggcacc ttcagttcag ggagaggcga 540
attgggcaca ttaatggcac attttagagt cctggaaaat cattagcttt acactgtagc 600
ttctgtcttt ggccaacatg ggggagctaa attgtggcac ataacaata tgggaatgcag 660
attttagatt ttcatgctgt cttcctgggt gtgttgaata aaggacgtgg ggcaaatggc 720
ttttcatagc tgccacagag tcagaaagtt tggctttcct gtgggggaag atgtaagatt 780
gaaggggcaa ggagagccca tgggaagatg cactgggcac ttatctgac tatcttggtt 840
gcactcttta tgacacaagg aaattatttg acaaaattca cttcaagacc cagtctatct 900
tatacacagt agtactagcc tctttcagta aaaagcatt agcatcaaac tggacogagt 960
ttggcacatt gccacaattt atcgtgagat ttaatacca agaattcttg gtaccttttt 1020
gctagtctag atttcatttg ggtcatgact atgtcagcac tgtttctatt tcaagaaaa 1080
aaatacgttt ttacagtag ggccattttt taattattca aacagggttt tattttatgt 1140

```

WO 2005/05597

PCT/US2003/027106

gttaatttgg aggatgttaa taaagttcat aaaatatgtg cagactatat aatttaaatgg	1200
aaaatagctg gtatttttta ttgtataac aaatagagaa ctgaccaatg tgccctcctc	1260
tctgtccctg gagtggccca ggtaaatcag tgcccttaag ctgcttttcc ctttcgctgc	1320
caagtctgca gaccggccca atatctgtaa atttaccttt gtaatttgcc atgtagtttt	1380
tgcaacaatg acctaattaa tttagcacg aacctatata ttgctactgg actcattttc	1440
tgtcacaaac ttaattttca ggaaatgcaa cctgacgaat aagaattctt tagctctcca	1500
catgtgttct ctgagaccaa aggcataatt aaataataa taataatac taaaatgcca	1560
gcattattaa aggcaatatg cttgatgcca aactcaattt gaagctagta aacatcaaac	1620
tgtattttcta atcagttttc gaatgtaacg tattccatat tgagtttgct ggattctgtc	1680
tctgcatttt actggccagc tgcactcccc tctgcatttt taaaacattt cagcaaaagga	1740
ttttgctgtt cttagcaggg tttagtaactt ggggtctatt tctgagctca ttctctatto	1800
tgagatggca ttgagttagg ctggcaaggg aaggatttga ggcatggggg ggaggggggt	1860
ggcgaggta cttctgatcc cagcagggaa taggtgagct tcatttgctt ttacaatagg	1920
cgacacagta ctgcacctg gaggggctct caggtgcgcg tcagatgggc gcattgtaaat	1980
gcccgtgcag atgtggcggt ggaatattaa tgcttctccc accgctgcac cataataaag	2040
ctgtacacag cgagcttaat atgcagctag gctaggggaat tgtataaact tagatagccc	2100
agtgtaaagag acagcgatgg aagaatgcgc ggtatgctac agttcccagc ttgttctgct	2160
ttgatctata gcaaaatgaa aacatcatct attctctctc gcagagttgt ctctcact	2220
ctgcgcctc ccagctccac tccagttagg attttcttcc cttttctctt tcttttctct	2280
tttctcttcc cttttctctt tcttttctct tttctcttcc cttttctctt cctttttctt	2340
ttttctctcc tctctctctc tctctctctc tctctctctc tctctctctc tctctctctc	2400
tttctctctc tctttctgct ggtatggaga aactcaacat aatttggttc atattggttaa	2460
ttacaggcat ttgaatattt aaaatttaaa atagccatgg ctccagcttt ttctgttaaa	2520
aagtatgtga ttgaaacaaa gggatttagg tgtaaatatt tgtgttgatt tgcaacaccc	2580
ttcttctccc attaaacaca cagcacaca tccacactgc tgatttaagg actcccatcc	2640
ctttatttat acttcttttt aaaaacctac tctcaattgg agcgccatta aaatactttt	2700
ccattatatt tttagtctg ttattgcttg aggttttata gagaattttt atcatgtgtt	2760



WO 2005/005597

PCT/US2003/027106

```

catttaacag aatcaacagc tgcagaacc agttgtgcta aatcc 2805

<210> 86
<211> 3481
<212> DNA
<213> Mus musculus

<400> 86
taaagggaagc ttcccatgtg gcacttagca tcatatgatc ctgagctcag gtacataggg 60
tcaccacact cctccctcga agtcacacac ctctccccc gaaggggagc catagtattg 120
aaggctcagt attggcacac ccacctgatc aggaacctgc tgtgaattct ctaagactgc 180
atcagccottt gtgctctttg ctgaaaagca ggcttgggct ttctttgctc ttacctttaa 240
ttacaggaaa aatgtcagcc tggttgtgoc aatggttcct catctcagaa gtgagacttc 300
aggtgatcc cctaagcaat gtgtaattca aggcaattcc ccagagtcac aggaagacac 360
tctccattcc aagaacaata ctctctcctt cctcccccct tacctcatt ctccgggtgc 420
cttagcgaat gtgaggaggt ctattgaaca tctaactctc aaatcaaagc caagcagaag 480
gggaacttag cctctggaag atgtattaca aagaagtgct agcttttccg ggctatttta 540
tgagggaaac aaattccagt cgtggataag ctagtcttaa atctaggaaa tcaatcattt 600
attcttttaa ggttccttaa ttacacctca tttagaggtc cttaaacctt tccaaagaca 660
ctgttacaat tcctcagag gcagtgagga atgagccagc ctgtgccgca gagagagatg 720
agcttccgaa gcagatgggc catggccatg ttctgagAAC ccacacctta gtgcattctc 780
agtgacagat cgcacagtgt tgttgctga gtagaactcg gccatgacat aacttttgac 840
caagctacca aaggggtctg gtctctgaaa acagcgtgct ctggacctgg cttgctggaa 900
gccagagaac agttctgtat tcgagtcctg tttcaatgtc tgctatcaag ataattgtaa 960
gtatctttct cctctgcagc ctcaattgct tagagtgagt attgtacaaa tgccagggtc 1020
tgccacagcc ccagttttcc catctgtaga ctgagggcac tttaatgtag cctatgtatt 1080
atgaggatcc agtgacagtg gggcagacat ttgacctgt aagtattaga tattcagggg 1140
ttggtggcct acttactggt agctctctct tatttttttc ccttaactt tctctcagt 1200
agattggtcc tcagctattg aagttataaa agttatcaaa taaagtccta gggactgacc 1260
ttcaatgaga cttgcagact ttctatatta ttacaggtct aatgggaaag gcgtggctcc 1320
tattgccact gatcaaatgc caaggaattt catgggtga agaaacattc atgatttaca 1380

```

WO 2005/005597

PCT/US2003/027106

ctctctttgc tctggaggag cagagccctc catcactcta gctggagggt tgggcttgac	1440
atttcaaatg gaagctctgt gaggagacac attgcctacc tgctcctacc tacacacaat	1500
ctatagtttg agggggctgc acacatccct ctttatactc aggaagacct ctgtgtgaca	1560
ttcaggccaa atctcaagat ttgaacttag tcacagttaa aatgttcctt ctccagata	1620
aggttgccac ctgccagggt ccaggaatta ctatgtggat accgaggcat ctatccatca	1680
tctgtgtgag ccgcgagctc taatgcttca gctgtcatta agattacca gatgtcagag	1740
caaggctact ttggcctagg ggagttttgt ggcctctctc aatcaagctc gccctccgt	1800
ccagagctgg cacaaaagtc cggaatggta atgccagaca gccatgaaga acaggatctc	1860
aatgtcctgt gaaagtacag cagctgtctg agtcatcga ggaaggtttg attaggttcc	1920
atctcaattg aagtgtacat tgttccaagt atttgaacct gacaatccat gggctacatc	1980
tagtctttat ttggctcagc tcaaaaggac tgctatgtag aagtccttca ttctaatag	2040
gaacatttga ttattacaaa ccccatocaa agtggggttg cacacaagtg gcatecatga	2100
ctttattctg gagtgatgca tacagctgcc tcaagccctc tgctattttt acctctacc	2160
ctcctcaata aagtacact tttcttttgt aagcatcaat taagtgcacaa ttgtgtattt	2220
ctcactggcc tgtgatacat taggattcgt gttataacag agggatgaac atgttttttg	2280
ggcctctttt gtgtctctt gggaagagct ggatttctg gtaagataaa aaaaatgttg	2340
acaaagaatc atggtacaag agtttactct ggaatgtgt ggtgacccat gcagaagggc	2400
ccaggctgga gcacacagct gtgtggctga agaggaacta agggcactat aggtgaaagg	2460
ctttagcctc atgttcaaa ggccctgaaa agtcagctaa aggaaagcag agccaggaca	2520
agattgttta acatgggcag attctatttt caggataaat ttggcagggg gcattggagg	2580
atgtcagga taggacaaaa acatctgctg gaaaaagggc caaccaaggt gatggtgta	2640
ggggctactg tggatctgta gtatgtgaga cctccaggga gatctttagg tcattgggag	2700
gttatccttg aagacaatta tgaactggag tcccaatccc tctctgcac cttgtttgtg	2760
ttgtaagtgc gtcacttcac ctgtgatttc tactgggatg tgctggcatt cttgaggctg	2820
gaagcagcga ggctgccaa tttgtaagta aaacctttag gaccatgaga taataatcg	2880
ttttttcttt ctataagtta gttgtgtcag ttcagaaaca gggaaatggat gagtgttaag	2940
cattaagttg aaaatcaagt gtatgtctcg tgccctgctg cctgcctgcc tgccctgctg	3000

WO 2005/005597

PCT/US2003/027106

```

cctgcctgcc tgccctgcctg tctgtctgtc tgtctgtctc tgtgtgtttc tctctctctc 3060
tctctctctc tctctctctc tctctctctc tctctctctc tctctctgtg tgtgtgtgtg 3120
tgtgtgtgtg aaacatacat atacctacat aaaaaaaagt aaggaaaagt gtgacacagg 3180
ataaaatcca tgagtgccac tgaaggagact agaagagact aagtctgagg tattggacaa 3240
acagctccta aacaattttc cccctcttct ccattgcact ttccagacag tccacagcca 3300
gcttcccttc tgacccacca gcctgcacat tattcccggt tcctaaggaa tgtgcttggg 3360
tggagatgga ccacccctcc acctctgggg aaaagcccca ttatcttctc aaactcttag 3420
aggcggttta cagcttaaat ccaactagatt cccctgctctg cccctgggtg ctatatccat 3480
t 3481

```

<210> 87  
 <211> 1469  
 <212> DNA  
 <213> Mus musculus

```

<400> 87
actttgggaa gatatcagag ctttgtgatg atcagtatac tgggggaaat tgtctatgct 60
taaatattata gtgctatttg gtttaacatc ggtttcacca acaggtgtaa tacatttctt 120
tttaagtaca tgtataaaag tagactttta tgacgaaaac gacatgcagt gccaaagtgt 180
tagcataggt gttaaagact attaaattat agcagaaaaa ggatatgaat gatgtcaatg 240
gtaaatagcaa tcattgaaaa attgtctata aatattagat attacccaaa tgtcaatacc 300
gtagtttttc aagagtttag aattaatctt agtcatataa atttgtacta ttgataatta 360
tttaataatt tggaggagtt tgaacagtta agctggttgt aaactgtgaa tttctaattg 420
taaatgttca tttctaattg aaattttttc aagaacagat ttcagcttca catactaagt 480
actgacaaat aaaaagtgta gaaatttagt atttataaga aaataggctc taaaatgtct 540
tatgcttttc tgtttctgct tagagtataa tggaggaaga cagtgtccc tgacctaaagt 600
gtttctaata aagagtaagt gtagagacat cccacaagac agcagcagtg caaggctctt 660
aggaaagtgtg tgcactgttg ctgtggtgat gtatccaagt caccaggagc cgtgtcctca 720
ggagctttcg gctctgttcc agagcttgag acagttggaag ctgggttcca tcaactgagac 780
cagatgtgcg taggggctgc tagtgtgtgt gtaaaactgcc cactgctgtt tccatgcact 840

```

WO 2005/005597

PCT/US2003/027106

```

ctcagccccc tcaagctgat cccctgggtc cccactcaaa gcacagacca ttaagcaata 900
aacaaaaatt tcattcaaat tataattgtg gttattctcc tgtgataaga ggtgctaatt 960
ttgtgtgaga agaacatgtg acctctttgg aaatatagtt tggaaagtaa gtttttcccc 1020
ctctcttgtt acttccattt tgtcccaaat tcacagtcca tgaagaaaaa gtaaaattgt 1080
ttaggagact tctaagaaga gctgcttgca ataacattt cagattttcc cgagtgtgag 1140
ttgggaaggt ctccatttcc tccatactga caagcctgt tgttccaaag tctcttagct 1200
tggagagtgt ctctacactg agtctcacct cagcctgcca gtgacctga ggtcactgct 1260
gaggaagaca caggagtctg cactagtctt tacaagagcc gttgtcattt caggtccccg 1320
gggttcattt acagtacatt tatacaactc acaagagtgt gggattccgc ccccttgagt 1380
atttttatat ttagtgtgat aactgcgcga gatgcattga ttgcacattt tgactctata 1440
atacttagta tgaaaaatta atttatgcc 1469

```

&lt;210&gt; 88

&lt;211&gt; 3497

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 88

```

aaatgaagga tgttttttaa tttaactttt tttttttttt aaagaaaaat atcagtaata 60
ggtcggcaac agcagccgta ggaagtacaa cttagggtag cattaagaca tactgtagtg 120
tggatatatt ttttttcttt tttaaaatgt gatattgaca ttttattaat attttttaaa 180
ttgttaoqtt tataaaattg gtaacttaag cacagccagt gtgaggcact gaaagcgaca 240
tttattacaa tgagctgtgt cactcctact ttataaaatt ttactaacia gttagactaat 300
gtagacatto acagacggga tagcgcagaa gcactctcac acgacaagtc tccaaaaaaa 360
aaaagcta atcagagagg cgaggaggaag cctgttcccc ttctaattaa gtgcaacctt 420
gttttatctt attgttttat tttttaagaa aggaatcat gttctttttt tatatctcta 480
tatataagat acagagtgtg ttgtaaggt ttgggggtgt ttttgttttg ttttgtttta 540
agtttccaaa caaccaact aagaaaaatg ctggatgctt ttagaataca aaacttactc 600
aagtcataaa ataacaaat agaactttta cttaagaaa caacaacaaa gagagagaga 660
gactcgattc ccagcaagtc agtgtctcac aagggcactg gctaattact ctctgtctcg 720
cgtgtctgat gtcctgtccc cagcccctgt ccactctccc cactctccca tcacctcata 780

```

WO 2005/005597

PCT/US2003/027106

gaacgctctt	tgttgatcat	tgtctgttaa	taatgtataa	aatggctatc	ttgtaagtgt	840
gctgtcttgg	tactagtgtg	gtgacttttt	ttctcctctt	ctagtacata	ttgataggta	900
taatgtaatt	aaggttttaa	aaaaataaga	catagtattt	cagattagga	ccagtaagga	960
tagaactttc	tcttatttat	gaaaagaaaa	aaaatgctaa	taatttgggg	gcagtttttt	1020
cctttttttt	ttttttccaa	gttcaaat	acttttattt	ttgctgattt	gatgtgggtt	1080
caactaacc	aaggtctcac	aatgttcaaa	tggcggctga	ctctacagca	ttctgtaggt	1140
ccctgcccc	ctagctgaag	gggtgtgcca	tactacctta	aatgcaaaca	ctagatatgc	1200
aaaactggat	ttttttaatt	tattttttta	aagagggagg	tgtggtatat	taaaatgatt	1260
ttactaagag	aaaaaaaata	tttttttaag	gatgctcaga	agaaattgat	aatctgtgtg	1320
aatatgtttt	agatgtttat	atacattttg	aagagaccga	gtagcccata	gcacaaatct	1380
tgtagaacat	tgatatgttt	tcaagtggct	acctaggata	aggttcatca	tttagtcccc	1440
cacccccacc	ccaccgccat	ctagaagtcc	atcttaaaca	attttttgta	aattctttca	1500
gcactgggtg	ccatctttgt	ctttgtttca	gttaagctca	atagcgaatg	tgggaccccc	1560
tcctctgacc	ttccctgggg	gagaaacctt	cttggctaata	ggctcttccc	tggcattatc	1620
aataaccacc	cggggactct	ctggctttca	gatccatctg	cctgagaccc	caaggctctc	1680
tcctccctag	aggggagggtg	gagcagcagt	tgactcctgg	ttccctccct	atttcagcct	1740
ggatgtgggg	ctggtggaga	tgccctccacc	ccaggagcct	ctgcatatgt	ggttcgtggc	1800
cttcttctca	cccattggga	aaaccaaaca	gcctcacact	ctgtcccat	cgctcattgg	1860
cttaactcaa	gtgagacccc	aactgggcct	ttgcgttttg	tttttgtttt	tttttaaatc	1920
cttcatgacc	attctcttaa	tttgaactcg	tagcttgggc	tttaaggtag	catggctcga	1980
ttgctgtcga	cttaatgttc	caactgcacag	caattcacgg	ccagtgaatg	ttacacacat	2040
cttgcctagc	tagtataaaa	atcattgggt	aattgttgg	tctaatagacc	tgaagggtgt	2100
tcagtttgtg	ggtttttttt	ggggggggct	gcttgggggg	ttgttttttc	ttcttgtgtt	2160
ttttttaatt	tgagaattta	gggggataat	ttttgggggg	gggttccaaa	taaaaaaata	2220
gaaagctatt	ttgatcttta	gtgcaaaacta	gggacgtagc	ctccatcacc	acaaccacac	2280
cgcttcgctc	tgccatccac	ccaccgcagc	agcatcttca	agaataaagc	aatatagttt	2340
actacatttt	tttttaaaat	tgaaggctcag	ccatgcttcc	tgtattatat	tgcatatgaa	2400

WO 2005/005597

PCT/US2003/027106

```

attgtttaca aaagaacac taactcatcc ttctctttat cagttgaaag tgacacacgg 2460
gacagagggg aattggaggg caggtagggg aggggagagg gtttttttgt attttggttt 2520
gtttggtttt ggtttctttt cttgaatgtg ctttagtagc cagatcctcc aagggaaggca 2580
aaagccagcc agccagagag agagtagcga agcgggcagg ctgcaggtaa gcacactgaa 2640
caagagacac actggcaagc tccccacct cagcgagagc agaaagcgaa cagctcagcc 2700
cagtcctggg cacagacact acacaaggca atgctggaat tgaacaata ctttaatacc 2760
gtttaagttt gtttctcttt tttttttctt cttttttttt tctttcacca agaaaagaaa 2820
aaagtaaact aaaatacaaa atacaaaaac aaacaaacaa acaacaaccc atataataaa 2880
aacccacccc tctctgggaa acaaccataa ttcaaacatg gctatttagt aatcagaagg 2940
tattgtctca gacaggattt catttccggg aggcagggcg tgagggggga ggggggtggg 3000
actgagagac agttccagag cctccaggga aggcttctac tgctaactgc tgtattctgt 3060
atatactgtg ccacctgtg tggagtctgt gagtgtgctc ttgagtagcg tgggctagcc 3120
aatctcccat tcatgggtgt ataaactcgg aattccatat gtaataggat gcaagtctaa 3180
gogtttcagt tggacataaa tgtatctaaa taaaacttcc cctagcactg tggctgacct 3240
cacccttact tttatacttt agtatgaaac tgatgagaac tttggtagtg agtatttttt 3300
ttatatatat acatatatat gtatctatat atatatatat atctcaagca tctttcaggt 3360
ctttgtgtgt ggctttctta aagccctgtt gtaaaaaaaa aaaaaatta ctaagtggat 3420
ggcagctctc cacatcacag atgtggaaag tataatttta tatttgtatt ttcaataaaa 3480
taagtttgtg aaaggct 3497

```

<210> 89

<211> 4277

<212> DNA

<213> Mus musculus

<400> 89

```

tttcaacaaa cattttggct caggatacaa agtttaaaact cctttgctag agaactttga 60
tagtggtatg ggatgagttg atcattatag ttttgtataa tgaatattgc acatgtatat 120
aaattactgg tctggggcag caacagggtat acagaagcat gagccttttag tgggcagtta 180
gtcagtggtg tgagtgtcgg tggagaatac atgaagcaaa gcactggggt ctcacgggag 240

```

WO 2005/005597

PCT/US2003/027106

gagggggagg atctgcaata ggagggtgcc attaactggt ttatctgtgg gaaagacctg	300
ttgtcttgga tgaactgagt taactggcca tgtggaatat tgcagaaaat aaagctagaa	360
atgtggtcat taccagagt gcagatacgt gagcataaga accatcttgt ttagactgcc	420
aaagtattca tgactttgta ttgtctgaag atctcattgt atgtggtggt gttatgggtc	480
tgtttgtata ttctcttcta atgggcattt tagcaagttg ctcacactgt tcaattttct	540
acccttttgg agaaatcaac attagtcctgg ctttaaagcc taaaacatac catcataatga	600
cagactttgt tagagaaaag cttagaagtc agctaatac tgaagtgtctg cctttgggga	660
gcaagcagct cctgtgtctc ttatatcaaa acctccaca ggaataatgt gttctggctc	720
ctcattgtgc atgacgcccc tcccagataa gaaacagtcct ggttttcagg ttctcattct	780
gacttttgag agcacaagat aaagatctta gctctacttg gataattgac tatagaaatc	840
agaattctca gaaatcaact gctttagaag gttaaaatgt gaagtttctt gtttgttttt	900
tgcttgtaact gaatattttg aattttaatc tacctcgtct cattttttgt agttaactct	960
gtcattgcc actgagcatg aagcttgact ttggtcgttg tctaaaatgg gatctctct	1020
gttcagtgac agttttttct cttgccttcc cttctggccc ccatttcacc taacatcacc	1080
tcttattgct cctgtcagaa atagtgttta aagtcctgtt ttatgggaaa aagtgttca	1140
ccaatgctgt ttgtctctga ggtcagtgag agaaggagtt aaaaacacagt ggtgaaggaa	1200
gggcagatcc tgcctctggag gcaaaagctg acaagggaagg agtcattaat tacagacaat	1260
ttcaaaagta actgattgtg atcattaatg tcacaataga tcaaaaccta attatcacag	1320
cctaggttaag agccatcagt attaatcgga aaatctaata ggaaactatt accaagaaat	1380
taggccaaat tgaatgcaat gaacttttta tcatcttttt ttggtaatgt ccttggtgtt	1440
ggcaactgtg accctaacag ctggtccaag ccagattgc taatttctact tttaaagagc	1500
ctaggctggc cctagtgcct gtagtactcc tgcctcagcc ttaaatactg ggattatgag	1560
gggatgtgtg cattcctgtt tgtgtgggtg ggtaggagag aattgaactc agggccttgt	1620
acattttaga caagtgtca accactgagc tgtattccta gttcagagtg ttttgtttgt	1680
taggggaagt tccagagaga ctgaacttga gctaacattg ctgaaacacc aacctgaat	1740
tttctcatca tggatttgtc cagtctaata agatcagtg gataacagg tatatattaa	1800
agtcatagag tgcctcgtg gaacatttgt gctgtatcat ccgttgagtg cttgtgtata	1860

WO 2005/005597

PCT/US2003/027106

gagctctgta ctggctgctg tgaaggctgt gggaggaaga cagtgtcctg ctttgaaatt	1920
ctttgagaac taaaagata gtttccttgt atgacaacag gaagaagatg caagccagtg	1980
ttttcctggt tgcagtaacg ctaggatttg atcctgaaca gcctggcagtg gtgcctgatc	2040
ccagtagttc taagatagga acaaatgat ttcacttggt aattctaagg gatggggaag	2100
atatctttgt tttcctttct gtgttacaag ttatatctct ggtagtagga gaagccatca	2160
gtatgtcctt aagatgtttg taaagatgct accacctttg ggtgagatga gtcaggcagtg	2220
ggaaaagtgt ctgtcctttg ggtgtcacag gaggaatgcc aggcagtagt agaggggaatt	2280
gtgcctagga gtctacactg tgccctgcag cctctgtgca cttcaggtgc ttcagtctaa	2340
tcttacttag gaagcccatg ctccctttctg gaacttgatg taccactac aagactgaga	2400
atcagtgctc tttgtttgtt tgggtttttt tttttttttt taagacaggg tttctatgta	2460
gccatggatg tcttggaaact tgctctgttg accaggctgg cctctaactc agagatctgc	2520
ctgcccctgc ctccaagta ctgggatcaa acatgtgtat caccactgcc tggctaacct	2580
ttcacttctt aagttagttt tagtgtttaa aatgcaactt aattttctaa atggcactaa	2640
ggtggtttgt ccagccttgg tttactccag atgagcagca gccctcaaca gtgtgttgat	2700
tgaactcctc tggctgcagt gaaatggctg aaagttagat tttctagtgc atacttctgt	2760
gctagctccc ctacttggtc ttaatggctg acctggggca agtctttcct tccaatgcct	2820
cagttcccca tctgtcaaat ggggtgataa tactgacctc cctcatgggg tgttgtgagg	2880
cattacagat cagagctgat caactccttt aggatgcct gtggaggata ccttcagtcg	2940
aaagtttttt agccctcact gagctacttc caagtttgga agtacttagt gaccttggtg	3000
agtttctgtc cccaatccct taacccctca tcaatgtgc tagttcagat gttgacagtg	3060
ttttgtgaat gttggagtct tgatcatcca gtctaacttg ggatgtctgt aggggaaggca	3120
cttgtgggct ctgtgtcttg catcacaaag agacttagaa attcaagagc cttgggttag	3180
ggaatcttga ggcaggagtg ctacttcctg tctttctctg caggcaggag ttaaggctct	3240
attctcatgg atgacttggt ctgattgtct tggtagtgtg gattgatatt gttgcttcca	3300
ttttccaggc tgacctagga caggctgtcc actgaactct tcatgctcgg atgcctctgc	3360
cctctcatag aagccagacg gctcaagcaa cataaacctc ccttccccta ccaaaaagag	3420
ctacattgta ttttgttttt tttctagaaa taggtatacc atttcagaat tgagcattgg	3480



WO 2005/005597

PCT/US2003/027106

```

tctctaaaggc ttcttttcag ttcaactgtgt gtggaatctg tcacctcttt tcagtggtata 3540
ccatctgacc cactgaggac atcttggaca ctgttttgcc cacctgaggg ttcaagagcc 3600
tttcttgctc tgtctcagta tagggactaa ggcattccca gattcttcat gatagggttc 3660
cttttccctc acttgacctt ctattggtag ccatgaaaaa gcacaaggtc ctagctccct 3720
gtagatacac actccagttc tgttgggtag actctactcc taacaggggt cctagaggggt 3780
tctctggagg atgggaaagg aacagttctc tgtcctgcca aatagtagcc agcagttgcc 3840
ttaccctctc ctgctggcca tgaaccaca ttctcacgga aagggtcttc agagaccct 3900
ggtttttctc agcaactgtac catttttgtt aggaagcagg tcacaccttg tagccaggtc 3960
taaatggaag tgagacagtg aattctctgt ggaacttttt ggtttgtggg ggggtttttg 4020
ttgtgtttct tggttctgtt tcagccaaac ttgtctgctt ttgatttctt taaaggataa 4080
gtggtctatc tatctatcta cacgtatgtt tgcattttta gtgtaagtgt tttgagaaaa 4140
aaaaaaaaca gacattatgt cattctacaa ctgacatcca attcagacat catcctctcc 4200
ccctccacc ctctttttcc tcttttccct cttttcatac tcttgtattg gttctataaa 4260
acgattgctt ttcaaat 4277

```

<210> 90

<211> 3887

<212> DNA

<213> Mus musculus

<220>

<221> modified\_base

<222> (3295)..(3295)

<223> a, c, t, g, unknown or other

<400> 90

```

tagcagtgac aggcattttt tggtagctt aggtactc acatttgttg cagcatgaga 60
gtttggaaga attggaagca ggtccaatct ctacottatt acttatttta atcaattttt 120
aagctcttgg cttttgcagt agaattccta gaggtttttt tttttttttt ttagtatttt 180
tatacatgga tataaaaaag aaagaagcca gaaggacaag tattattttt ctccctacaa 240
aaggaagaaa ttaagagact atagttgtca gatacaaat ttaatatatt aattattttt 300
gattattttt taaaagaaga gaaggggata atggctggtg agacttgata ataaaaccaa 360
atgtagacaa aattatcggt gtaggagaaa agtgaaaaaa gaaaccagga acaagtagt 420

```

WO 2005/005597

PCT/US2003/027106

taatagaaat agtatctccc tctttacatt ctctcatcca agtggtgtgtg attttaaaac	480
tgttaatctc tcagggtattc tgcagggtcaa aacacatcct tgcttggaagaa aaacaaagtg	540
tcaggtaaga cagctgtaga gtagggtacca catatgacta ggggtcaacc actgctcata	600
agaagtctcg atgcataag gataaatata cagtgttctc cgtgggtgagg gtaactcggt	660
ttccatctcg gttacactaa gagcaagcat ctaagtggca tctaattgggt cagaattaga	720
gttttctgtc ctcattttgt gttgttagtc acagggaag ccttcctatg ttaccagctg	780
gttgggtcac tcccttgtct ccttgtaact atcttctaga cagattctga aaaagagaat	840
ggaagaaaaa gttttaaatt gttttctggc atctggcaaa ggacttgagc atgccttttg	900
gctctgatag gcacttgtaa gcagacatct aatgaggcta ggctagtgtt tttatcctct	960
aatcaggctc tatcttactc tgtcttgctt tctaaatcct atctctaaac aacaccaagt	1020
gtcttatctt tggatgggag gataagtga ttagaagtcc ggcctcagtt tgggaagagt	1080
tctcaatatg aaaggttaat aacaccattc ttacagaaag aaaaaatca tccattgccc	1140
aaattgggaa gccacagaaa atgcttgagc taaccaaaa tcccataatc gattttctat	1200
tcacttaacc agtctattca cgcaactagt cactagctat gttctattta aaacagccac	1260
cactaatcag aatttcactt tctcacctga gctaacatta ttcactgatt ttggttgga	1320
tatttctcta tgctgtggg ctctctttc tggctctctg aaatgatgat ctgtttgtga	1380
ttacagagct cttatttgga agacagtga tcagcagcat tactttgctg tgaatatgga	1440
gaatcagaaa tcttttagtga tttcaatgta cgtagggtata tgtttttata cacacacaaa	1500
taacatacag ccttggtgat tcatggatat tttgttattg tttctagggg gctttattat	1560
gctgtagtac atttactcag ctattaaaaa caatgaattt atgaaattca tagacaaatg	1620
gatggatctg gaggatatca tcttaagtga ggtaacccaa tcacaaaaga acacacatta	1680
tatgcactca ctgataagtg gatattggcc cagaattttg gaataccaag atattacca	1740
gatacagtc acataaagct caagaagaag gaagaccacc atgtagatag ttcagtcctt	1800
cttagaaggg ggatcaaaat acctatggga ggaatatagac aaagtgtgga gcagaaaactg	1860
agggaaaggt catccagtga ctgtcccacc tggggatcca tcccatatac agtcaccaa	1920
ccagatgct attgtggatg tcaacaagtg cttgctgaca ggagcctgat atagctgtct	1980
cctgagaggc tctgccagtg cctgacaaat tttgtttctt ctaatacata tctgtggcta	2040

WO 2005/005597

PCT/US2003/027106

aaattagtc	acatagetga	gttctacatg	tctcagatgc	ttattgtagc	gctagcactc	2100
atggaaatat	gtgttggtgt	tacttctcag	gtataagatt	cagcctcttt	accoccttttc	2160
tccatggtag	agttctagga	cataattgta	ttgcctcacc	tggttggaatt	tcattccatc	2220
ttgatgaaga	gtctggaatg	ccacagattc	aattattgtg	gctcataaat	agctggagtg	2280
gtgctcattt	ccctaagtct	tacogacatt	aactgatgaa	tctacacaaa	cactctttta	2340
tcatgacact	ttatagatga	cagactgagt	gtggaaaggt	tataagattg	ttcgggtgtt	2400
gtgatacgca	gggacagcac	tgacgtgcac	atttcagctg	acagctatca	gtgagctcat	2460
taccagagag	cagagtcatt	catagattat	gtaccaggct	cctatatagt	atacatgag	2520
attttattca	gtgtgttttt	taaccttgca	aataattatt	taggtacttt	tacttcacag	2580
gcaactaatt	tcttttctct	tccttctctg	ttgtagccat	ctcccccac	tgctctccca	2640
gtagtatctc	tctaggtcac	tcaggctatc	tcagaacttg	ccatgtagcc	taaactggcc	2700
tcaagtttgt	aatcttgctt	tcacctccct	agtctggaa	atactgacaa	tcattttata	2760
gccagaattt	tatttcattt	gaaatgtcag	gtttcactct	tgccacgtag	gctgatgac	2820
ctcagtttga	tccttatgtt	tcttagtgaa	aggagagaa	taactcctga	aagtcactct	2880
ctgaatctat	acataggctg	gtacacacgc	acgcgtgcgc	acacacacac	acatacacgc	2940
acatacacac	acacacacat	acacacacac	acacatacac	acacatacac	acacacagac	3000
acacacacac	acacacacac	acggcaagtt	gactgaaaa	tttttgttat	tttctcgggt	3060
ttttgttttg	atttttgagg	cagggctctc	tgtatccaag	gctgacctca	gaactcactgt	3120
gcagccaatg	atgattttga	acttctgctc	cttctgcctt	taatttccag	agtgctcaga	3180
gcacaagcat	gcaccacct	acttgccttg	tacactctcg	gagatcaaat	ctagggcctt	3240
gtgcatgcta	ggcaagcact	ttactactaa	gtcacacacc	taccogtgg	ctacntgagg	3300
ccctgctctc	ctatcttttg	ttaaagggtt	tgggtccatt	ttgttctact	agggagtatt	3360
ttcaacctct	acctctttct	gcctattagt	actocaatat	ctaaggaaat	ttgaagagggt	3420
cctttctaac	ttaaagtcct	gggatttagc	tcagtggcag	gatgcttgct	tagtattcac	3480
aaagttctgg	ttcacttcca	agtactgccc	attcaagcat	acggagtaac	agtaacttga	3540
agatttagca	tagaggggtg	tgttatttgt	agagcaaa	ttgaaatcct	cattattttaa	3600
ctttcttcaa	aggaagtgtat	atgggatctt	gataaagaag	tggaaatact	catgtaaaga	3660

WO 2005/005597

PCT/US2003/027106

ggaagagtag atgataaagc caattactga gaacctgtct gtaatcttgg agtaataata	3720
gtgtgaactt tggctagatg cactcattca ttcagcaatc attgattgac tattatgtgt	3780
aagactactg ggtaaagagc tatgtagtgt ggacataaaa tacagaaatct gtgcttagag	3840
aatgtataat caattgacaa gttagtttta tggatggata tgaagac	3887

<210> 91  
 <211> 2219  
 <212> DNA  
 <213> Mus musculus

<400> 91 ggccagttaa cttttctggt gccaatgtga actttaaatg tttttatctt acctgctttg	60
tggatgaaaa atatttctga gtggtagtgt tctgacaggc agatcatgtc tttttatctt	120
gtttcaaaa aactatttct gattttgtaa aatgaaatc aaaatatgtc tcagatcttc	180
caattaatta gtaaggatcc acccttaatc cttgctagtt gaagcctgcc taagtcaact	240
tactaaaaga tctttgttaa ccagctattg taaccatctg tccgcttacg taggtaaatg	300
tagacgctgt gtgtatatgg cttgtagtgt tagtggtggc tctccgtggt gagattcttt	360
ctcagtgctc tctgtgtccc tacaagtctc atgtagggtt cgatgttagg atggttaaga	420
tgtatatagt acaaaatggt cagtccttga ttgtttatg tttgtttgtt ttcatgacta	480
gtaatggtag tggatacttt aaaaatattt tctgaagatc cttaaaacct tggaaattgt	540
aacatactga gaagagtggg tgtttgaata tttttaacaa cttgtataag tcaatatgaa	600
tacaatcaaa agctaaagtg cttcatagaa caggggatct accttaagta attatcatga	660
gagacctctt gtaagactgt gtctatttta ctacagagaa cagtttgaga gtgaaactgt	720
tacaatttag actttttgtt gtattttcta agagaaagag tattgttagg ttctctaac	780
ctctgttgac tactatggtg agtgatgtta ttttaattgc aaatttaaat agaaccaac	840
agaattaaat aactgactgt ctctctctct ctctctctct ctgtctctct catgaaaatc	900
cttagttctg tatactgect tctgcttaga tttagttata tgatcattag gttacatttg	960
atctaagttg actaagattt caatttcaat ttatatctca agcattctgc caggggaatag	1020
ttttaaaaaa tgtttccaag gcacttcagg tacaagtcac ataggtagtt tgtttaatct	1080
agtccttagc ctaggactca aggactgaat gttttcaaat aacacttttc ttgttctcag	1140
agcctcagtt catataaact cttttaaac cgtgtgtgtg agagttaagc aagacctctt	1200

WO 2005/005597

PCT/US2003/027106

```

ttcttgtctt catgagttgc gaaattgaat tcattggagct gatgtggcta acaagtttat 1260
tttaggaatt gtttagaaaa tgctgttgct tcgggttctt aaaatcacag cactccaact 1320
ctaatacaat tattggagac ttagcagagc tgggtctgaa tcacactaaa aaaaaaagg 1380
tactggatcc ttccagtat gggtgtgtaa aaaatggcca ctoggaaggc cacagataa 1440
cgggctctga atcaccacc ctagagagct tcagtgtctg cgtgctgatg gtcttttctg 1500
gtataaagtt cattctagaa ttttgaagta accaccggt ttactacata ttagtcatgt 1560
gaattttgaa gttattttgt aatagttaact ttcatttgtt atttactgtg ttgatcaaga 1620
tgtgtgtgag tgtttagcat ttattaaagt attgtcttct ctcctagact tttgcctctt 1680
cctgtagtta ggggttagagg tgagggtgag ggagtgact caatgtgatt cgctggggta 1740
ggacagtttg ttgtcttgtt agtcacagtg tggtgctctg ttttttattt tagtaagatt 1800
tatattttga gctctctgaa tggaaagtc cactgcaacc ttagctgcac gcattgttcc 1860
cattagacct aagtcttctt ggacttctga gtcccagat actggataaa ggaagaggag 1920
agatggagta gcctgtctgt cactgctatg agagaagcaa gaaagtgggt agagaatac 1980
ttcacatttt agtcacatct tctcttttta aaaaggtagc catcagtcaa ggaagaact 2040
agtcaaaaa aggcctgaca acctgaattc agatcccag aacgggcata aaagcagcca 2100
ggtcatgggt agtgcactcc tttaatocca gcatttggga ggcaggggta gacatatctg 2160
ggtttgaagc cagcctgac tacagagtga gttccaggac agggaaccct gtcttatto 2219

<210> 92
<211> 3433
<212> DNA
<213> Mus musculus

<400> 92
ttttataaac agctcaatat aaaacataga cagtgtttga ttattttcct tgtgtaagtt 60
tgatttaaaa cgttggaat gtgtgctttt tagtgtttac taaagtata agaaaaataa 120
gcattcaata cactatagat tcaaaacat aacattgcac caaatagaaa tgatatattt 180
attatgcaat gccttagtca taaactgggc tcaaacatc ctgagctaa aacactgtt 240
tcttttaata tgcttcaac ccaaggcct ttcctctcag tatctgtcaa acttgaataa 300
cgtcttctct ttactattac acacaggcca gcctattaac ctgtgtctta gaattgttgt 360

```

WO 2005/005597

PCT/US2003/027106

atatagtctt	tttaa꜑atcc	atagggata	ttttgaatt	ttttggtgag	tatttgttga	420
atttgagata	gcatacagta	gatgtttaag	aaatagtagg	aagtcogggtg	agacgggtgt	480
ttccatcaag	aactcctagc	actgctgtaa	atatcatggt	gcctactgga	agggaaatgta	540
gatgctatgc	attttggaaa	taatctgcat	ctgttaaacc	tgcagaagtt	ttttaatgcc	600
actttaacac	taatgcactg	acagattcta	aatattttgt	gagaaatggt	gaaatgttta	660
acctgatagg	cttctctata	aaagagtgtt	ttgttttttt	ccotgcacca	caagctgtgt	720
ttatcacttt	acagttgcat	gttcaacttg	tcatagctgg	aattactgta	taaaaagaac	780
tgattgtgac	ttgtagttct	tctctagagg	atgctgctag	aacgtggttt	tgctttgcat	840
tttgtagtto	ttcccgcoag	tgctgtgtgt	agtctgctt	cttcagttct	gcagatttca	900
ctagaggcgc	cctttgcatg	ttgcaactcg	ttctcatttg	gaggttggac	tcagaccagt	960
tagcacagta	ttctctcato	tgtgtcactt	tgtaaaacta	actgtactct	gtattttotta	1020
tttgtacata	tcaatgtgag	aaatctcctt	tttttatggt	gcaattacct	tgtgatcagg	1080
cagcttgagt	gctatgcaaa	tagtaagtag	tgtagtgggt	atttttcttt	gcattgttgt	1140
tgtgatatac	ctagccagaa	atagatgtgg	cttttgtttt	gggggcagat	tactttcaaa	1200
agcaaatata	attcacttga	atttgacaaa	ctgaagcaga	caagtgttct	gggtctctcg	1260
ataatttggg	gtgtttggct	gtcagctagg	ctcatgaagt	ccactgtact	gtaatgatgg	1320
tatttaoctc	tgtgtctatt	taattaccct	cgcgtctgtg	gaactgctga	tttgagtagt	1380
gatttagcatt	tagaaatttt	gtaatgtaga	gttttagaga	gagcactttg	aaagataaac	1440
attttattat	gatgggtgcta	ggtacaaaa	ttatagcatg	ggatgtgaag	aaaaaaaaatg	1500
agaaccattt	gaaaggaaga	aaggaatttg	ttgtctgctt	ctaagctaga	tggtttgttaa	1560
aggttctgct	ctgccagtgt	tcagtatcag	tggctgaatt	atggataaga	actgtagaga	1620
atcttctggt	tagtccatgc	tttttatgta	gaattgggtt	tatctaatag	ttttactatg	1680
gaaatgcctt	ttgatatta	aagccagatt	ttagaggttt	gatattgttg	gtctcaggag	1740
ctcaaaagaa	gtagcttttt	ccagtgtctt	ttgtgttact	gatttgggaa	atggtgaaag	1800
attggacagg	gaagaatagc	gcttggtgtc	ctcatgggtc	tctctcttta	ccttagtggc	1860
ttgacagtac	ttactatagc	tctgaggga	agccaatcaa	cttctgtttt	cctacctgac	1920
ctgcagggca	tgatggatca	gtgatgaaag	aattgtagcc	tgtggcactt	tgttttgacc	1980

WO 2005/005597

PCT/US2003/027106

tctggatatg aactctgact tttatagttt taaaatgac aatcttttga tgaagtcag	2040
ttttctttct ttaggatca gaagattttg cttattctg aggtcggact agggccaagc	2100
aagcttttct cttcatatga gctgtcatac tgtattttga cctctttctg cagcaaaaaa	2160
gaaagaaaaa tgacagctgg aaaaagtcct ttgtattggc acatgataaa tcttgatgac	2220
gggctatatt ctgaacaaac gctgtcactg accaaagctt gtgttttagc gtgttttagc	2280
atagggtgctg tagttggagt gggccccacc tctgctcctt tcaagtgtct tgcgtgtcaa	2340
gttattctct tcagacatcc tccattgtcc caccgactcc ttggcagcag aatgctggca	2400
gcttgtagcc ctcatgttct ctgtaagtct gtttcattgt aggggtcata cctgcctcag	2460
cctgacagga gtaggtttct cgcaacccac tgtgctgaga cagttgatgt gatgcaaac	2520
attcttggag tgtgttgttt tctttggccc aagggtaaac taaaatacct gtgaactgca	2580
aacttgcttg tgattgaact ggtgcaatac agttccttct taaacgtttc tgggtttagag	2640
aatactcagc catcctggaa actagcaata tttattttgc ctcatctact ttattttcag	2700
tttttagatga ggtgaagggt ttcttttcagt tagggactct ggcaaggctc attctagtgt	2760
agctgaagag gaagctatac tattttctgt ttactgtatt ttgctcccta ttttatgctt	2820
tttaaaaaat ttccacagt actcacttga ttgagcatat tgatttgaaa gagctaagat	2880
tttcctgctt aatgtcagcc attggctctc ctgataattg ggactttttg tttgtttgtt	2940
ttttgttgtt ttgttttttt tgtttccctt ttccctaataa ttataagttt agagaatcct	3000
gtaagagggg tgggtgcatg tcttaatgct gagaagcagc agctttgggg ttgaatttac	3060
ttgaatgggt taaaagatt gcattgttac aaagctagaa aaaatttatg tatgaaaaat	3120
gatcctagcc ttacactgag tacaataata cttataagca tgtgaagatg tgacttttgt	3180
gatgttactt gtacaaacat atatacatat ctatacatat cttttgaagt gttgaaagga	3240
atagtacttt atattcttta tcatacact tttgtaagtg ttgaatatat tgcgttttat	3300
ttttctatgt tctgttttgt agccttaaga agtgtttcaa acgatctgaa tgtataaaac	3360
aagtcaatgc cctacatggt gtgatgctgc attatatata caaccgtgtg catatattaa	3420
attctgtttg tcg	3433

WO 2005/005597

PCT/US2003/027106

&lt;210&gt; 93

&lt;211&gt; 2228

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 93

```

gggtgtccgcgc gccgcggggt ggggcagcgtt cttcaaggct cagcctccct cctgcgggct      60
tccttgtgctt ttttttccct ccaacccttt ccgcgatcac gggtttctgg tacccaatat      120
aaatggggcga cagcgaaccg gcctttaacc tttccttgaa ttaatgagct tcaggttcag      180
cttcctocta ggtttttttt tttttttctt ccttgttttt aatgaacctt cccaactcct      240
tttcctatcc ctgagagcgt cagttacttg caggaagcca ggcctttccc aagctctgtg      300
tagcagggtcc cctccaacc ccaacctgt ctcagccaat cgcaactgtt ggacgtcgta      360
gcaaatttgtt tgggtctctt tggcagaaca agagtctatc cgaagcgcgt tagatactca      420
gatgacaccg aggtccgtag cagatgggtg gactgagaag gtacctgoga gctcccagcg      480
gaattcgctg gcagctgcgt gaggtctcgg tgttttggtt tctttgacat tttccagct      540
tcaaagcgga gaacgggagt cagggtattg gcgaacttca acgtgttcgg ttacaaggta      600
attagattaa tgagagtggg gagtttttat gcagtgcaat tatgccacga tttctgtgtg      660
ctcggtggtt tttccacaag tttccagctt attaaattaa tccaatggta ggtctgtttc      720
tacctgactt gtctccaaa acctggggca aacccctccc aactatctcc aaggaaaagg      780
gctagtaaac ggagacaaa gaaagcactt gtggaggagt tgacgatagg atcccatttg      840
tcatcagata gtgtgaagtg gcctctcttc tggagagtgg cgtcagtgct cctaagagcc      900
acgttacttt cccctgcct ctgccattct ccaaaactgt gaggactggc atttaaaatg      960
cacttagcgc aatctaaatt acagtttgca acttcacctg ctacattacc cagatatctt      1020
aattaggaat ctccatcaa ctacaggcac attaatatcc cactgttac agtgtgtcga      1080
tcaatgacca aggataattg gggggcaagc cttaagtctc cccatcttat tcattagaca      1140
cactgtggat tcotcaaacc accagatccc taatgaagga gacctgtctg ttttcaactg      1200
aatttttcat tactatttac aggcattgat gattcaagtg gtaaacacac ctttcaactac      1260
tcaagatata tccaagcct tatgtctatc tttaatatgc ttaataatag cctcagagtt      1320
gctggaggaa atgacttttc atggggggag ggctggaaga atctgacagc tttacataat      1380
gggtgtactt aaatgctatc aggacaaaca tttttaccat cttgcagtta ctacatataa      1440

```



>400	94	
acagaacaaa	ctgcattaga	atgcaaggca ataaagcaaa aaactagaaa catcctggac 60
aaataaatatc	tagcagttta	attaaacaaa agtagtccaa catgtgcctc agaaatagtt 120
aagtttttaa	gcatatgttt	ctgccaatgt accaacacaa gatggactta ataccacaaaa 180
gaaaaaaaaa	acagttcaac	cttttttatta aaaaaaaaaa aagaaaaaga aaaagaaatg 240
acagcaaaat	ccctaaaaaa	aggataatta acttttcaat ggcgactata ttacataagt 300
ggacagtaat	ttccaagag	gcacactaat gggggcacga agtctgctac aaaaatagctg 360
agacaaaaa	atgtacotca	aatgttttg caggactaca ctgtcttttc cttcagaaga 420
ggcttttgta	tgtcttctta	ctcggttag ctccatcttc atctgtgcat acttacgctg 480
cactgtcaaa	cagtaacaaa	aagccctaat caaagtgaga aacaatacac ttacctctgt 540
ctgatctgag	gtcttatcag	atcagtttta attgacactga ctgtcacctt cagattttaat 600

WO 2005/005597

PCT/US2003/027106

gtcttctactg	gtccattga	cctcattctt	agtgtcactt	tctctcgatt	cagggtttgt	660
gtcttctactc	tgtttttctc	gactactgga	cttcacacta	ctctttttat	catcagatcc	720
cttctttttct	gccataaaa	aagacattga	ccatggaatt	tacagtgaat	cacaacaaat	780
ctactactat	ttaaacagg	aaacattgag	agcaagaac	catttccac	ggctgtgaga	840
cagtctgcag	agctcagtc	tgctcagctg	agattacaga	gggaaagggc	aagaagacca	900
aaaagaaca	gaaaattctc	tcaaacctgc	tagagtcacc	ctataattga	caacttcagt	960
aaatttcatt	ctagataaag	accatccaaa	ggcaacaaga	aagacaaaag	acaaatacac	1020
aaaacggta	acatgggtta	attaagttgc	aaggcaaat	ggcaccaga	aatttaacat	1080
ttaaatgaca	cgtttattaa	aagaaaactt	atacatattt	aaatatccaa	gagggggcac	1140
acctagtaag	aaaatgagat	cttcaaaaaa	atctaaaaac	caaattttgt	gttttctgta	1200
atgaaatcta	agaggttttt	ttcctaagg	aaaaaatata	agctgagttt	ggaggaaaaa	1260
aaaggcagca	gtttccagct	ttccctagag	ttgcattaga	aagggtaaaa	agcccatgtg	1320
aaaggaaaagt	gtcgtctgcc	ttccagctgt	acattacatg	tacctctaca	aaaggattct	1380
gcaaaactat	taaacacacc	tttccataaa	agctattttc	cccttaaaac	taagaacaat	1440
tcattagttt	gacaaagtag	ctcataacag	gaagatgtct	gaagagaagc	actctccaga	1500
cagtgtgtac	agacacaaca	tcaaacacct	ggaaggagga	tgggagcaca	aaaaccagtg	1560
ctgtggactt	gcactctacg	aaaggaagga	gtgtgcatac	ggtccagcct	ttgtaaacca	1620
agcacagcac	tgtctaaagt	gttaaccata	gacttgcttc	ccagctgtct	gtccacctgt	1680
gggaactatg	ctctaactga	ccttgtggga	aagtctctcc	tttgagcctt	atgggcttct	1740
cgggtgcaca	ggtgacttca	atgaggaaga	gtcgtcttgt	tgctccgtag	aggactagta	1800
gtccaaaaat	cttatctctt	ggcctatgta	aatatggtag	atcttaatat	tcttaaggat	1860
atccatgtgt	gttggtattt	agagttagg	attaaacaga	aactctctga	acagaatata	1920
gatacctatg	ggtagaaaa	tactccccct	ttgttgagtt	cgtttagggt	cttctgttat	1980
gattacatca	cgtggagcag	tgaacagtct	tactcatctg	ccattattag	atgtttgtta	2040
gtacagatgc	ctgatgccca	caggccagaa	tgctatcttt	gtatattcag	aagtgtctag	2100
aacttcctca	agtcataaga	ctcatcattt	ctagaagtct	aaagtttacg	ttaattgctat	2160
aatggcaggc	ccaacataaa	taggcctgct	aagttttttc	agtatctagt	cttctctttt	2220

WO 2005/005597

PCT/US2003/027106

```
ccctagtctc accaggaaac ttcagaattt tactaaattc aacttgtcac aagtcagtaa 2280
tcaggacatg tttttgcttc aacacaaaat tatacaaatg ttgtctattt aagtggaag 2340
actggaanaa aacaattaat aaaacagaaa tatgtaatca aaagcttcac aatacatggg 2400
tgattgattt gatctgagt aagagtcac aggtaactct tcaaaactga tctcacttaa 2460
aataatacaa agccttttcta aacaaaacat agtacaagag gagacttcac agaaacaatg 2520
tctgaattat aataagcaga ggc 2543
```

<210> 95  
<211> 2305  
<212> DNA  
<213> Mus musculus

```
<400> 95
acagaccttt tgcttttctg tttctttgtt tttttttttt tccatctca ccgtctcact 60
tcacctgtg gagaagacct ctccaccctc agagccccc aagaagagag agagaaagca 120
ggtgctgtct ctcttggccc tctaccgggc ttagtgggc tctttggcag cctgactctg 180
gatatgaact gagaccatc tttgaactgg acacgaacta taaaccagtt ctattctggt 240
ctgtgctggt ttgttttctc ttgatcaaaa gccaaagaaa atgtttttgg gaatgtggaa 300
ggccactctg gacatacaaa gcttcctcag gttcagtggc tccgtctccc ccatctctcc 360
ctgtcagcta tagcactctg cagatctctg atagtctgat ctttggggat attgttgtga 420
atcatgggga cacttatctc acagtgaact gccatacgcc agccatcttg ggtcaacctc 480
ctatgtatct ttctatgat gctcctccga ttgtccact ggggaagtca ttcactggct 540
gaacatctga ctgctgtctc ccagccact gaatccagag aatgggtggg accccatgtc 600
cagctgatag atcatcatat cacacaggct ctggagtcta gcagcttttc accaaccagag 660
aggcgttcat tgccttttta aggacgccgg agtgggggat cttcattctg cttttagcat 720
gtggctgcct actactgttt gccttacatt ctgctctggc tctctctgga atcttccctg 780
gttcttccgt acctttcccc caccctaatc tcagactaga agtgaggcca taaaccaaga 840
aactatgagg acatccaggc tatctagctc atttgaagg agatggacat tttcttcccc 900
tgtgcaattt ttgtgagtct tcagggtgtt ccaacatata tctagaaga tgaggtgcca 960
agaactgccc agcctctgac tatagggcac tctaccctgc tgtgtgtcgc tcaattcttg 1020
```

WO 2005/005597

PCT/US2003/027106

```

aaccttagat ctttccttcc acatgattgc aagtggtccag ttccggagaaa aatgccaaact 1080
cctcccccac tctccaggaa tatcttgaa ctttattttg actctgagat ctggagacaca 1140
acagaaactct gtccacagca ataatccact cagtactatg ggatggatgg gttagaagat 1200
gcgttactga gcctgagact ggtcagccag ccaactggaca tgcgacctgc ctcttgtatg 1260
ggtgcccttg acaggttgac actctggtgt atgttacaag acaaagtgtc gcattgtgtg 1320
aagtggtctg cctggggctg tgggatgtgc tgctgttatg aatttgagtg gaatggggga 1380
tacagatgct gggtatccat ctgtagctca ttgcagttag cgtgatgaca gggggcacgg 1440
ggattatctg tgtagcatag gcattgtgacc ttgactaag ctcttaccoc tgcactgtaa 1500
tgtgtctgaa tgtctttgta gacctgaagg tgcacttaac taaactgcct actaaggaat 1560
gactctcaco tgggtccact cactctccct tccaggtgtt tgccttttca cccctctctt 1620
aggatttagg ccttgatagc tcaagcccca atgctaagac cgtttttctc tgtaaggaga 1680
agacttatga tatactgata gccatagccc atctcttcca acatgtaggg cctcattgtc 1740
ataggggtgc cttggaagga tcaggtcaco ctgtgggtat tagccatccc agaactctct 1800
aagtgcttaa ctcacttcaa gtgatctgaa tcagagagac caaagatatt aattttctct 1860
gtcctcagat ttctagaaga cagactatgg ccaggaaagg ctttattttg gtttgggctt 1920
tctctctctc ctttctccat ctgtacacat cccctacctc actcccactc tgagacctaa 1980
attttgaagc tcaatgaccc tggttcactg gagtggtgtt ttgggttagt ccagaatatc 2040
aggctcaaca atttccccc cactgtatgc aatggacagt cattttctct aacacaaaac 2100
tgtgtgggtg atttagattc cactgaggtg gaactgggtg tgccacagcc ttgatcttct 2160
tgagactaga cagaacaaga gtgggtggctg agaaatacat ttctctaagt agaaatgagg 2220
tacaacctat aaaggacttt cttcacagtg agcgtagcag ttacgacttt ttcaaatagg 2280
agtcctaaagg aatcagtaaa gaagt 2305

```

```

<210> 96
<211> 2771
<212> DNA
<213> Mus musculus

```

```

<400> 96
gctctcttga cagatgcacc ttcccggtgc cctcagatc tcatgacac tcctgtttct 60
gctggggatt accatcttcc gttggaagaa ctgcttttag gatttcgtga gtgtgagcct 120

```

WO 2005/005597

PCT/US2003/027106

gtggtggtga attctggaga gctgctttgc ctggagcggg tctgctgatg ggggaattcag	180
acaggcaagc tttttcattt cgacaactta ggctgtcacc ctgctagett gcagottgct	240
tccttcttcc ttctcaggga gagttcagct ttcagccctg tttttgcttc ggaagataa	300
caatgtatca ttttcttggt tcttttttta cagtccccc ccccaagtgg ggggttcagag	360
cctgggctca gggcaaaagca ggcagtttaa gctgccttcc gtctcccggt ggtttttcca	420
gaaggtatcc ggggtgtggt tctttgtttc aatcctgctt ggggttcag atcttccac	480
atctgtaagc catgccttct ctggattta gaagttctta atgggttagtc ctcaaacaca	540
gctccagcac tttctccggt tccctcttgc tgggctgcag ttacacctgc ccacgtggta	600
gggtgttccc tggtaagcca cctcttctgt ttcccttata tgcttagatt ctgaccttgc	660
cttgccgato ccagctcttt agcccagaat gctactacat ctaaaacaat gtttgttcag	720
gttccacaat taagtcctta actcattagg ggctgatccc acagctgggt agatccaggt	780
ctgatttcat togtttgtac acagacatcc aactttccca gcggtttgtt aaaaagccca	840
ccactacccg atcttagcat gtttgtgtgg ttcctcttag actgtctgct acattccaat	900
gtctgcatct ctctctctct ctctctctct ctctctctct ctctctctct ctctctctct	960
ctctctctct ctctctgttt tttttctatg ctaataccat gctgtttgat ggctagaact	1020
ttgtaccata gtctaaagtc aggagaaatg tctcctgctc tattctttgt gctttctggg	1080
ggagctgttt gggttgtatt tgggtctgaa gtttgtgtga gtccacacac agttggggat	1140
tgtttcttct agttctgtag agtccoctgg gcattgttat ggggatcatt gcattgaatt	1200
tgtagatcgc agcgaccgt gtgcattgtt tagcagcact gagtcttgta gctgcgaaat	1260
gggtatttcc cctttctccc gtgggctgtt ccacttctgc ccacttgctt tataattttt	1320
gttttaacat cgttcaacttc ttttaactaa cttgtttcta attgctctac tactgataga	1380
gcaattaaaa atgattttta ttcttttcag ctaagtcctt attggcaggt ggaagagcca	1440
ctgtcgggct ggggtgtgtg cctgtggctt tgctgggggt tttagttgta atcatcttga	1500
gtaacatctt caagggatcc tgtatatatg tgacacgtgt tcgtccttga acactaacat	1560
catttctcat cctttctggt ctgggtctct gcattactat ctatctcgta ggaacttccac	1620
tgttgaaatg agtaagtgtg aactggagtg agtgtgccct ggagtaagtg tgcctctggag	1680
taagcgtaac ctggagtcct tgtcagggtc tggctccctg ccttctcgcc agcacacacg	1740

WO 2005/005597

PCT/US2003/027106

```

ggctctgcgt aaccgcagac acggactttg gaggccaaagc tcttactgtc acaggcatat 1800
ttctccttgg cctactttgt gctgatgcca cccccatca aggcctcccc agtatctacg 1860
agaccatcat gtgggtttat catctcttct atagatgggg tgcactgtat ttgtcaattg 1920
gtatacgctt agccatcctt gtctgaaact gtggaattac taggagaaat gtaaaggaaa 1980
tgtgtcaaga cattagctca atgtctcttt gatggtgacc cccccaagc atagcaaatg 2040
gacaaacggg atcatgtcaa actacgaagc ctccgtactg cagaggaaac aaccaacagt 2100
gtgaaaagac catcttgcaa acagggagga aatgccagcc aatcacacat ctgatgatta 2160
atagcagaac atgtgggaaa taaaatctct ctctctctct ctctctctct ctctcttttt 2220
tttttttggt ttttcgagac agagtatttc tgtgtagccc tggctgtcct gtaactcact 2280
ctatagatca ggctggcctt gaactcagaa atctgcctgc ctctgcctcc caagtgtctg 2340
gattaagggt gtgcaccacc accacctggc agaataaat atcttaattg caataaaaac 2400
caatttgaaa acaggcaata gtaccaaag ggtgaccaac aggtacctga aaaaaaagt 2460
tcaatattag ggaacaaaac caaaactaaa atgagctagc ctcatgtact ggctgttaag 2520
cattttctta attagtgtac aagggtggag ggccattgt gagtgggtct atccctgggc 2580
tggtagtgtt gggatttata agaaagtaag ctgaacaaac cagggggaagc aagccagtaa 2640
gcagcattcc tccatggcct ctgcactcgt tcctgcctcc aagatcctgc cctgtgtgag 2700
ttcctgtcct gacctccttt ggtgatgaac agcaatgtgg aagtgtaac tgaataaacc 2760
ctttctccc c 2771

```

<210> 97  
 <211> 1629  
 <212> DNA  
 <213> Mus musculus

```

<400> 97
aacctggaaa cgtctaaaaa tgaaagcaac tctcagcaca catacacaca ctcaacaaca 60
taaagtaaac aactttttta caaagggaaa agtagattgc atagtttcag ctatgtgtccc 120
tggaactaac agatccacct cctggggcct cccaagggtc ggaagggaag tcggtgttaa 180
agggtgtcca caccatatto cactttatta atgttccaag tcctggctg tcactaacca 240
cttttaaaaca cgcattggg atcgtcttgt taaggcaagg gctgggtggg cggtgtggtg 300

```

WO 2005/005597

PCT/US2003/027106

```

tattgttgat tcttgtctcg ggggttgatt ggtcattttg tcattttgaa aggtgtgctc 360
actcatcac acaagcacac accgtgtgtg ggaatccaga gtggcttggg taagaggggt 420
tcttccagat agtttgcttc tgtttcaccg tcagggtatt tactgacatt tcttggctcc 480
ggagctttag atctcaggag tagtgtagat tcccgagagc agcagagtct ttcaggccgc 540
agtagacctg ttctctctaa tctgtatgct aatgggcata atgttgaaatt gatgcccott 600
aaaatgaaag ctgcacctgt gtctcactgt ggtggcaggg taaagggaga tggcatttaa 660
tgcttctctt gtgctgtttg caagcctaata accacacgtg tgtgtgtgtg tgtgtgtgtg 720
tgtgtgtgtg tgtgtgtgtg tgtgtgtgtg tgtgtgtgat ttgtattgta tatacaaagc 780
caaaactact ttttggtttc tgtaaactgc tatgaaactg ttctgcattt cagctttctt 840
gtgtattttg taagaattgt taaatggata ttggcatct gcttgactgc agtaaatcag 900
gcggatgtaa tgaacttaga atgtctgtaa gcaagtgttg atgtcttcatt ggaaggagga 960
agaaaattag ctaatgatgt ctagctaaat gaattttaa tttgtttttg tagttaatcc 1020
actgaagagg ttggaatagt tgatccattc ttcacccttg aataatatcc tgttaacaga 1080
atataattcag atttcttcag tggctttgat aaatctatgt caaaattttt cagataaaac 1140
cagaagctgc tacttgaaa gtgaaaaaga ctgagttaga aaatctttct gacaggtttg 1200
agtgagacgg gctgttacca ggagcccatg agtgatagtt agatttatag gttactaaga 1260
atcagggtatt ttctttatgc tgagtacctg acatgtctat cagcagacc tctgattctt 1320
acaacaaaaa tttgtaatat tctgaoggt gccacagatt atctggagaa aaattacttg 1380
cctgaggaca gaagacattg cacatgtgtt cctcacagaa gctgctagaa aagaaggagg 1440
cagcatgtct gtctgtctgc agtaaggag gcagcactcc tcttccagcc ctatgctgct 1500
gtaccctcta aatgggtccc agtcagggtc taaggctaag gtcactatag cgttcaatta 1560
aaacagggaa aaaagggtgt gtccctagaa atccatctca accttagatg tgataaaagg 1620
aataaaacgc
1629

```

&lt;210&gt; 98

&lt;211&gt; 2277

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 98

```

attttttttt cttttttttt cttttcttct attttttttt ttaaaagatc cagccttaat 60

```

WO 2005/005597

PCT/US2003/027106

aaaagggtgt attaaaagca cctggctagc atgtgttatg caaaaaatag cagagacaga	120
ctgactgtca atttgattgc ctatttttat aggaaggtaa aaatctgaat tactaaagaa	180
atttagataa agtccctaaag ctaatttggtg ttaaatgttt taaagatctt attacctgtg	240
agagatctgt gcattgacct tttgaagttt acgtaaattt aagagcagag cttaaaggctct	300
gtgccataggt ttgaggtaat gagcagcttg agagggtttgt acttttcttc agtggtgtct	360
tctctgcttt taaaacactc agaaatatcc ataccactgc cagttcattt taaagcatct	420
gtgagcaggg tattttttga aaggatatcat tgggtgttac cacaactggt gttagtcttc	480
agaaatgatt tttcttaagt gttaaactct gttgaaatgc aattaccttt taatttgagg	540
gttgatctaa aatctatctt ctgtttttgt atataggctc tgtaagtttt tgtcattttt	600
tagctttttt taatagtcca attacaatgc cctaattgta agctgtgtgg acatacatgt	660
gtttacaagg gggattagtt aatagtgaga ttaacaggta agtacaatgt ccatagatag	720
aatttctctg aacattttaa aaatggaatc aaaaaatata tatacttgaa atgaaactgg	780
agattttgta ctaattttaa tcttttatta ccttttattt tttcttttta aaaaaatcag	840
ttggaaccct ttgtttgctc tcttatgttc acacttcttg cttggcctat ttcactcata	900
agcgactttg gatgcagaca gtgtattagc cttgcttgct gctgctggtc cattacttta	960
agtggtgtta ggaaaaata aaatagcttt ggttgtctc attttgcagt gtctctacc	1020
tgataacaca tgaatgtata gcagtaaaag taaaattac aaacctgttt atttgtcaaa	1080
gcctctctgt tgtctaggag ccagtttcat ttgaaaaactg gtttttaaatg tgtaaaagca	1140
atccaaagag atgaaatctt acagacacca aaaaagagag agagagacaa acaagtcaga	1200
gagaagaaaa aaggagttaa acacgtgtag ttcatataga gaggcagtga cagcttgagc	1260
ttgtcttgag tccagcgtc gctcagtgct gtgtagtcac attccttgca gctagtagtg	1320
agattccaca aggtatttct cctgacgtgg cactttgaat tcaatatact gctttgaggg	1380
aaagggaata gattttaga aaggattcct tcagtgtaaa ttacatgtg tttatgtttt	1440
gtcagtttct atcagcaaga tgagcaagat tctaagtgc ttgccatagt tgttgatcat	1500
gtcaggccat ttcatgtctc cttaacctat aatcttaagc agttaactac aatttggaat	1560
ttacaaatag catgtagctt aaggatttat tttaatttga ttctcctatg gagactgttg	1620
ctttagtttt tactagttta aagtcagttc taaaaataaa catggacgct ttcataaaca	1680



**PCT/US2003/027106**

```
<210> 99
<211> 2518
<212> DNA
<213> Mus musculus
```

174/186

WO 2005/005597

PCT/US2003/027106

acaagacatc	aaaagacttt	gatgatagtc	ttgttgaaaa	actgaccatt	gaagtacccc	840
ttgtataaaa	tctgtgtgta	tcttgggctt	caccctacc	ccacatgct	agcttctaaa	900
aagatttacc	aggaacccag	ttttaaaaat	tctacttaga	gtccttggtt	tattggtata	960
tcgttagcat	ttctgaaaat	gtttttctaa	aagtctatat	aatttatcta	actcttagta	1020
atgcctaatt	aagtcaactg	ttacttattt	atgtttccat	tattccaaa	gaaaccagca	1080
tgtagaagac	tcctctgggt	gaaatagctt	ataggttata	tgtaactttt	taaaattgtg	1140
cttagataga	gcattttct	catgcaacga	tcttgtatag	tgtgtaaggt	gctctgtgcc	1200
cctctgtttt	ttccctcat	cctgaaggta	aggactattt	ccaaggcaaa	tgtagtgtaa	1260
gggaattggt	tctgaaagag	gaaaacttac	tggttttcaa	ggcccagcta	gggtgtgttt	1320
ctaactctct	tgsgaagttg	agagcaggaa	ggtaacaaagg	ttcttctctg	cctctgtccc	1380
ctttatcatg	taaagaacaa	ggatgaagga	ccatgctctg	aaataagaaa	agaccgtcct	1440
gaaatactca	tcactctgtct	tttttattag	aagtcaattt	tcacttgtct	ttccaaataa	1500
gagagacott	agaggaagtt	agctgaacat	ggaaatttaa	ttctttgggt	ttttttttct	1560
attaatcatc	agttcaacct	tgcttgccat	taagtttggt	agttctgaac	acctaagtat	1620
ttgtggctta	gctattatgg	atacaagata	tttttcagac	cagcagccac	gttctgtggt	1680
ttggcagaaa	atgatagtgt	tgtagtccaa	gtagcagtgt	attttcccta	taaagctcac	1740
actagcaccc	aagcagaatc	atagcatcag	ttaaaccata	actgcagtgc	aagaatgata	1800
atgcactctg	gggtctgagg	catatcagct	cttgtttcag	agcatctgtg	ttactcagac	1860
agaacacagc	cagacagttt	tacaggctcc	agcacctctt	tcttaacctc	attcaccag	1920
gccaggcagc	tggtaaatta	gcagaagtct	cgccacccat	ttgacatccg	ttgtcatcat	1980
gccttcaga	ggactctatc	aagccacaaa	aactaatccc	tgccatatta	cagagggtact	2040
ttgtcactgc	acttctcttc	agaactccat	tcactcctca	tacttaacag	gactgatatc	2100
tgaggctatt	ctcattctgt	atctatagtg	ggcatcttat	agcagttggc	tcattgcatg	2160
tggagagaat	gtcagtaaat	acttgaatct	gcattggcagt	ttgctgacgt	gtatgcaaga	2220
gcaaggagcg	aggaatgcag	caagttactt	gtacatacag	taggtttcct	taggtcttgt	2280
gggcacatcc	cttgtaattt	atatgtatat	ctgttgtaact	gaagcatttg	gggaaatact	2340
tgtatagaaa	gtatgtatgt	catatgtcaa	aggaaatgct	ttctgtcccc	tgccaatggt	2400

WO 2005/005597

PCT/US2003/027106

```

gtattttgtgg gtattttatag ttgtatgtat gtatgtacat caatgtgtag attgtgtatc 2460
agtatatggt atatgtatgt tgaaattatt tttgtctttt agcaaccagt ataatatg 2518

<210> 100
<211> 1950
<212> DNA
<213> Mus musculus

<400> 100
gaaaatgtag aagacggaat caatgaaagt tcattccggc aggagaggaa aatcccatcg 60
aagaagggga agagctgtcc ctcccttagcc cccccgggga aacgagcccg aatcccgccg 120
tgagccgcag ccgatgctgg cagtctgcac cgggtgagga ggggcagaaa aaaaggcatc 180
tggaggagga ggagcgcggg agcggcggg gcacgagaca aaagcccgct caagggttgc 240
ccgctcccg ggggagccgg ccagcgcagc ggccgccaa aactcaagcc caactgtggg 300
gccgaggggg ccgggctgga cctgggcgag cggttctggg cgttccggcc gccagtgggc 360
acgggcccgg agagctggga gctctgccc gcaacctcac agcctcaggc gcggctcgcc 420
cctctccagg cgtcagcat cctccgcgg cctcgcgctc gcttcagcgc cctggccttg 480
gccggggtcc ggagcaccga ggctgtccc tgaccgtccg gctcaggag ccccgccagc 540
ctccgtgtgc ctacgcagc cccggacgct ccgctgcgc gctccagcct cctccgcgc 600
cctctggagg agctagggta acggcctcgg aaccgcagt cgcgagcaca cccgcggccg 660
gcctggcggg cagagcgcgc actccctcgg ccgagtatc cttccgcca ctcgccgcc 720
tcccgcgct ctacctctg attgtgggag aagaaaaccg ctgcaagagc gcgctcccgc 780
gtgagcgcg ccccgccgg ccgcgcgcg ccagattct ggccgagcgt ggagcgcgg 840
acgatgcagc tgcgcgggg gcccgcgct agtccgcgc ccggaaggat gccagggtgt 900
agggggcgag actgaggaac cgggcaagc tgaggaaccg ggtctgtctg cttgctcgt 960
catgtctaat tatggtttct ttcctcctg agcgcttct ttcagtgtg aaggaagg 1020
aacgaaaccc atcttttttt taaacacgag ggggtgcagc atctcttctt ggacactttg 1080
atttgctctg ttaaacatgc tttctcgccc cctaaaaggc ctaggaaaagc tgcagcaaga 1140
agcaaaagca catcttgggg ggaaggaggt tgtttttgtt ttccgctctt ttcatatata 1200
tatgaaatat ttatagatat aatatatatt tatataattt atatattata tatatatgaa 1260
atattttata gagtcgagaa taaccaagc tgcctttcaa catgggattt cctgactgga 1320

```

WO 2005/005597

PCT/US2003/027106

```

gtttccatga tgcaggcatt attttttgac ttcttggtca ctgggaaaaa aaatccaaat 1380
tgagagccac aagagaaaat atttagaat catccaagtt gtgtgacaaa catttggttaa 1440
aaatcattta tcttatgtac tagagggccc atcaaatat gacagttcca cagcaaatata 1500
aatgttattc ttcctcatat ccatagcatg tccaggataa gatggaatag aaaacatctt 1560
tttccaaaca caatatggta ttgtgatatt acaatgcatt ttatgtttgc acagtgcctta 1620
caagtaacct tctctttga ctactcatat gttaaatgat atctattttt gtatgtttta 1680
tttttcattg attgtatgaa tttttgcctt ggatgtatgt ttcttcccca cttatgtgcc 1740
tggttcctgt ggaggtcaga agagggcaat aggttccctg gaacagaggt tagaggcagc 1800
catgagccac tggatgccac gaatacaacc ctggtcctct gcaccagcaa ccagagctca 1860
taaccactga gtcactctct catctctcat aatttaaggt aacagtaaac atgtttttatc 1920
atatactaaa ttaaacacca caatttcttc 1950

```

&lt;210&gt; 101

&lt;211&gt; 3530

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 101

```

gtgtggccac tgcaggtgag aagtgcccaa agggagaaaag tccagaagct atgatctccc 60
tcccttccct gcttgctcaa gtgcctgtgt ggaagattgg gtcaatcagc tctcaacagc 120
agcatgcaga aatgcagcaa gtctgtctgt cccctgaaaa tgatttagta ccgaacagct 180
cctccacatt ttcatacagt catctcttgg gtacatgcc tccctagagc tttggctcct 240
gcctccccc acctcaggac ctatgtcaga ggttgtttgg cggtgagttc tagtgagtc 300
ttttttcctt tctttgacat gcctgaaaaat gcttctgtgt gtgctgtcca gaggtggcct 360
cgaagaagtt ctggctctgt gagtaaggca gaggaggagc ggcaccttc tagtgggaag 420
taaataggcg ctttgcttt cccaaaagca aacccaagga actcttcagc gtcttggaag 480
atgcattctc attcgttaaa ggccgagtgct tgactctggg tttgaaaact gcattttctt 540
gaggcaggtc tcaggcttta caagtccaca ctatgcaaga agagaggcaa ggaaggcgag 600
gaaaggcgat ccggcgagg gtgggggggt tctctagccc ttgtttttag aagggtcatt 660
gccagcgctg gttatgattg gcagctgatg attaggaatc tcgacactcg tatttcatgt 720

```

WO 2005/005597

PCT/US2003/027106

ctgagaagaa caccatttcc tgagagaaga cgaacaggcc tagtctaccg ccggcgtagg	780
ttttgtcata gatgggtccc gagtcaacca tgattttctt tccctcatac atcaccactc	840
tgatataacc ggtctttggc ctgtggtcga gacgccatct gtatgcagtg aaattcttcc	900
agccgatgtg gcgagggtca tgccacaggg tgccacactg gccaggggtg tttcctgtgt	960
gccacagtgc attccgcagg tgctgccag ggccggtggg ggagttcaca accttacag	1020
acaggcctga gtatccctga gcccttgtgg ggttggtgtc ccagtaggac tgggtgaatt	1080
gtctccacat cacaacgtag aagcggctgc tggactggta gccgaaaaca aagccagcgt	1140
agtcattcat tctctcggtg ttgatgaaga aggtaccgct gaagtcacaca gcaataaact	1200
catcataacc tacagcaagt ccagggtcac agtttacagt ctggacaagt tctttgccct	1260
gatgggggac aaccaggtta gggtcatttt gggagggtcc tttgggatct agaggaaatca	1320
tctggaattg tcggaaatcg gtttcaactga tgtcaaaatt ctcaggacag atgtcatcaa	1380
tatctggcac attgtcatgg tcaaaagtgt ctttgcaggc gtcacctcgg ccatacccat	1440
cagagtcctt ctggtcagga ttgggcacca gccctgcagtt gtctctgtca tcagggatgc	1500
cgctattgtc atcgctatgg tcacaggcat ctcttttgcc atctttatca tggtcggcct	1560
ggttgccatt aggcacatag ggacagttgt ccagattgtt ctgatggcca tctcatcga	1620
tgctctgatt gttgtcaca gtgtcccta tgaggtctga gtcagagtc agctggtctg	1680
gattgtgttc cagggggcag ttgtcacact gatctcaac ccataccatg tccgtgtccc	1740
tctggtcac gttgtaaac tactggcagt tgtctcgttc attgaggatt ccatacccat	1800
cgatgtccac agcacaggca tcgccctccc cgtttttgtc tgtgtctgct tggtcagggt	1860
tgtggttgta .ggggcagttg tcacagcggg ctcacacatc atctctgtca tagtcatact	1920
gggctgggtt gtaatggaat ggacagttgt ccctgtcacc ggggatcttg tctgtgtcat	1980
cgctcatcat gcaggcatcg ccaatcccg ccttgtcata gtcttcctgc ccagagttgg	2040
gaaggttggg gcagttgtcc tttttgcagt ggtaggtgtc gttggccaca cacaccaggt	2100
tttcattagg ccagcgcctc aggtctgtgt cctctccgca gatgatgcca ttgcctgcac	2160
agccgggctt gcactcacag cggtaacatg ggtcactgta gtgaccacag tagttgcact	2220
tagcgttctt gttgcagca tgcgtcccg cgtgcagggt gtttcgggtt ttgcacacct	2280
gtttgttggc catggcatgt tcgacacctc ggcgaagggt ctgtgagcca gtgaatcgtg	2340

WO 2005/005597

PCT/US2003/027106

gtgggcaggg caggcagttg tagccaggat ctgtgttctt gcaccgatgt tctccgttgt	2400
gattgaagca agcatcaggc acttctttgc actcatcgac gtcttttgca tggaatgccat	2460
ttccactgta gccaggagga caccgaccac atttccagct accatcaggg tagctagtac	2520
acttggcacc agcaaaagcca gggattggac aggcattccat caattgggca gtccctgcttg	2580
ttgcaaaactt gattttttctg tcacatcgcc aacacagtct ttgcctccaa actgggggtgt	2640
gggggttgta cagagtcggc tgcgtctctg caetctctct ccacaggtga cagagcagat	2700
gtcccatggt gaccagggag ccagaccctc cattaatgg gcaggcgtct ttcttcagg	2760
ctttggtctc ccgggcttca ccttcacagg gcttcccggt catctggggg ctggggggagt	2820
tgcagagccg gatccttgtg atcacacogt caccacaggt cacagaacag gacgaccatg	2880
gagaccagtg actccagcca ccatactgtt taaatctttt gtcacactcc tgaatgtggc	2940
aggtccttgt ctgtaccgaa gagccctcgc atctgttgtt gaggctgtca caggaaacgac	3000
cacgttgctg aattccattg ccacatgtgg cagagcagga ggtccactca gaccagggag	3060
accagccatc gtcagcagag tcgctggggc agcacogtgg gcagcattca ccatacggaa	3120
ctgtggcggt ggagcagggc atgatatggac aggacacctt tttgcagatg gtaaccgagt	3180
tctggcagtg acactctgtg caactgtcta cagtccactc ctcgttgttc ttgtactgga	3240
ctccatttgt aaagcagagg ggaggcogct tcagctcact gaccagctct ctgttctctt	3300
ccgtcacttt tcggatgctg tctgcagag tggtaacgat ggtgcgcagg cccttcagtt	3360
ccaggaccat gctgtagtag tcatcacagg agaggccaca gatagcttgg aggtcctttg	3420
ttttgtggcc gatgtagtgt gtgcggatag caggggctgga accgttcacc acgtgttgt	3480
caagggttaag aaggacgttg gtactgtgag tggagcagcc tttgttctg	3530

&lt;210&gt; 102

&lt;211&gt; 1857

&lt;212&gt; DNA

&lt;213&gt; Mus musculus

&lt;400&gt; 102

tatatgtatt aattatcgat ttttccatct gctgaagatt ttccgtgtta tagctttaag	60
attaactttt acagaagcaa tttatttttc aaataagaaa agtatatata ttattttacca	120
cgttaatcag tatatcttct tagctttcac ttttaaaaaa aaaaaaaaac ctcttcttta	180
tctgggaaat gtcaaaactt acacagactt gaatgtgtga ttttgtgata gaagctttta	240

WO 2005/005597

PCT/US2003/027106

gtactgactg tctttttatt gaagtttgcc agcagtggtc acttttgcg aagctgaaaa	300
gccttagatc aatgtgttga gcaatagctg gtagaatatt ttaataacat acataaactt	360
aatggaagga gagcaacaca atgaaatata aaccagtttt tctcttgaaa cttgcttgag	420
ttagttaaca aatctgttga ctagtataat gcctgggtga actatagcct tatttatgca	480
ttggatatta gaactataac cttattttatg catcagatat tagaaactta ataaaatttc	540
agtttgatac tctcaaatta tgggattttt atttttgtaa tttctaaatt actatctaaa	600
caacaaaata cacacttgag ttaattagac atttttcatg cactgtttat gaaggaaatc	660
acctcttcat acaatgagtg tcatgtctac tctggaaaatt catgtcatgc tagttggcac	720
cctgccttcc ttcatgccca gcattttaat gtttgagaac ttactgcaag catttgtgata	780
gagttagaaa gaacctaaaga cgcactaaag ggaggccagc ctcagccagt tttgtgacct	840
tgacagtcag gtcacctgaa tcaccacaca gcctatggtg tgaataactg aagagacatc	900
ctctcgaat cacttttaga tagtatttcc ttgtggccac tatccacctc catggctcca	960
tgtagtgggt aaagatcagc tgtgtctct gccacagtggt gttgcctctg tggtaagatt	1020
gaaaggaaat gtgtgtacac agaggaccat tggtaagaag gcagtgagtg ggagcctatc	1080
tcagcggagg cgtgggctga cagtgatggg ggcacagtga ggctgcatat caagggaact	1140
gtgaaattta tatgtattta tacgtatatg tgtatatata tttatctctc tctcacatat	1200
atttatctct tctctctctc ctctctctct ctctctctct ctctctcaca cacacacaca	1260
cacacacaca cacacacggt tctgtgttca tgcacactgg aggaaggact caaattttat	1320
tacagatggt tgtgagccac catgtgggtt aactcatcac atctggaaga acagaggaac	1380
agccagagtg gtcttaactg ctgagccatc tcttttagtg cccccccccc cccataactt	1440
tttaagtaaa gagagtactg gggaaggcga gcagattggt tgggagatat acaggagccc	1500
gcatgggaaa cagcagtggtc tttagattga gagagaccgc cgggtgagag gagaggtgag	1560
agtttaggga gccatggtac tgagtttgat acagaattgg agagaggata gagagtgtaa	1620
gggtattgtt ggtgttgcca tcgttggtat agttggaagg agtgggtttt acgggggact	1680
attatagtaa aagagtaatg atgaatttac aagttctctt ttgttcattt taaattacga	1740
aggctgtgtt ctgaacttta ccattagagg agccacacat cttgaagaaa tattttatct	1800
ttagaggaag agttgaagat ttttagactg ttggcaaatt gaaaacagta actgatg	1857

WO 2005/005597

PCT/US2003/027106

```

<210> 103
<211> 4304
<212> DNA
<213> Mus musculus

<400> 103
tttttttttt tttttttttt taagactgca gataatcttg ttgagctcct cggaaaatac      60
aaggaagtcc gtgtttgtgc agagcgcttt atgagtaact gatatagacag tgtggctgct      120
tcactcatcc cagagggtcg cagctgtcgg cccatgaagt ggctgcagtg cctcgtgaga      180
tctgctttgt tttgtttgga gtgaagtctt tgaagggttt gagtgcacct atataggact      240
gtttttaaat aagtagtatt cctcatgaac ttctcattg ttaagctaca ggacccaaac      300
tctaccacta agatattatt aacctcaaaa tgtagtttat agaaggaatt tgcaaataga      360
atatccagtt cgtacttata tgcattctta acaaagattc tctgtgactt gttggatttg      420
gttcctgaac agccatttcc tgtatttgag gttaggaggg cataatgagg catcctaaaa      480
gacaatctga tataaactgt atgctagatg tatgctggta ggggagaaag cattctgtaa      540
agacatgatt taagacttca gctctgtcaa ccagaaacct tgtaaatact tctcgtcttg      600
gtgcagcccc gcccttttga tcacacgatg ttgtcttggt cttgtcagac actgtcagag      660
ctgctgtttg tcctcttgca gatctcacct gtccccactg cacaccaccc tctcgcctct      720
tgcagacctc agcatctagc tttagtgtga aacagttcag ggttcaggtg acttctttaa      780
aaaaaaaaaa aaacctacc tcttcagaat gaggtaatga atagttattt attttaaagta      840
tgaagagtca ggagcgctcg aacatgaagg tgatttaaga tggttccttt cgtgtgtatt      900
gtagctgagc acttgttttt gtccctaaag gcattataca ttttaagcagt gattctgttt      960
aaagatgttt ttctttaaa gtgtagctca gagtatctgt tgttggaatt ggtgccagag      1020
tctgcttaat agatttcaga atcctaagct taagtcagtc gcattgaagt aagtagttat      1080
ggtaaacact tgctagccat gatataatc tacttttttag gtagtggttt ggcaaaactg      1140
tatgccttca aagtgagttg gccacagctt tgtcacatgc acagatactc atctgaagag      1200
actgccagc taagaggcgc gaaggatacc cttttttcct acgatttcgt tctttgtcca      1260
cgttgcoatt gttagtacta gtttatcagc accttgacca gcagatgtca accaataagc      1320
tatttttaaa accatagcca gagatggaga ggtcactgtg agtagaaaca gcaggacgct      1380

```



WO 2005/005597

PCT/US2003/027106

tacaggagtg	aaatggtgta	gggaggctct	agaaaaatat	cttgacaatt	tgccaaatga	1440
tcttactgtg	ccttcgatgat	gcaataaaaa	gctaacattt	tagcagaaat	cagtgattta	1500
cgaagagagt	ggccagtcgt	gtttaactca	gctgggataa	tattttttaga	gtgcaattta	1560
gactgcgaag	ataaatgcac	taaagagttt	atagccaatt	cacatttgaa	aaataagaaa	1620
atggtaaatt	ttcagtgaaa	tatttttttta	aagcacataa	tccttagtgt	agccagaaat	1680
atttaccaca	tagagcagct	aggctgagat	acagtcagct	gacatttcta	gagaaacctt	1740
ttctaotccc	acgggctcct	caaagcatgg	aaattttata	caaaatgttt	gacattttta	1800
gatactgctg	tagtttagtt	ttgaaatagt	atgtgctgag	cagcaatcat	gtactaaetc	1860
agagagagaa	aacaacaaca	aattgtgcat	ctgatttggt	ttcagagaaa	tgctgccaac	1920
ttagatactg	agttctcaga	gcttcaagtg	taaacttgcc	tcceaagtc	tgtttgcaaa	1980
tgaagtgtgc	tagtgctact	gactgctcca	gcacatgatg	gaaggcaggg	ggctgtctct	2040
gaagtgtctt	ctataaaggg	acaatagaat	agtgcagagac	ctggtcagtg	tgtgtcagct	2100
ggacactcca	tgctatggga	cttgcatctt	ctgtcctcac	catccccaag	acattgtgct	2160
ttcctcagtt	gtcctctagc	tgtttcactc	agacaccaag	atgaattact	gatgccagaa	2220
ggggccaaaa	tgggccagtg	gttttggggg	ttgtatcagt	tgactggaca	ataactttta	2280
tagtttcaga	tcattttattt	ttacttccat	tttgacagac	atttaaatgg	aaatttagtc	2340
ctaacttttg	tcatttgaaa	ggaaaaatta	acagttccta	taagatactt	ttgaggtgga	2400
atctgacatc	ctaatttttt	ttcttttcag	tgggtttgca	gcgaggggtc	tgtatgcact	2460
aggcaagggt	tctaccacta	agccacattt	cccaggaat	aaaatgttaa	cagttaaaac	2520
atacacacaa	atacacaaac	accttattac	cactttagta	aagtgcagag	tgctgcgtct	2580
ttgtctcagt	ctccacagtt	tcagctgccc	cttgatgaa	taactcagtc	tcgctaaact	2640
gtttactttt	atttaectgg	tttgactagt	tgcatctata	taaccagttg	tgcatgagga	2700
caacagccag	tgtgttttgt	ttgtttttgg	tttttttggt	tacatttttt	gtaaaagaatt	2760
ctgtagattg	aagtgtctct	tgaaaacaga	actgagatat	atttattctt	gttagcatca	2820
aaaaacattt	tgtgcaaaat	atttgccttt	cctggcaggc	tgagtaccat	atccagcgcc	2880
cacaattgcg	ggttcccatc	taccatgtcc	acaggggaga	cagacgggaa	gcacatgagg	2940
ggtgtgttta	cagagttgta	ggagttatgt	agttctcttg	ttgccttgga	aatcactggt	3000

WO 2005/005597

PCT/US2003/027106

```

gttttaagac tgttgaaccc gtgtgttttg ctgggctgtg agttacatga agaaactgca 3060
aactagcata tgcagacaaa gctcacagac taggcgtaaa tggaggaaaa tggaccacaaa 3120
taaggcaggg tgacacataa accttgggct tcggagaaaa ctaagggttg agatgaacta 3180
taatcacctg aatacaatgt aagagtgcaa taagtgtgct tattctaagc tgtgaacttc 3240
ttttaaatca ttcttttcta atacatttat gtatgttcca ttgctgacta aaaccagcta 3300
tgagaacata tgccttttta ttcattgtta ctaccagttt aagtggctaa ccttaatgtc 3360
ttatttatct tcattttgta ttagtgttaca taccaggtat gtgtgtgtgc tgtactcttc 3420
ttccctttat ttgaaaacac ttttcaactgg gtcctctctt tggccattcc acaacacaac 3480
tttggtttgg ctttcaatgt caccctattt gatggcctgt gtcccagtag cagaatttat 3540
ggtattccca ttgctggctg ctcttcacac cctttgcttc tacagcactt gtctctccta 3600
agatagttag aaactaactg atcaggggat ggacttcacc attcatgtg tctcttcaat 3660
tctattaaat agaccactct tgggctttag accaggaaaa aggagacagc tctagccatc 3720
taccaagcct caccctaaaa ggtcacccgt acttcttggc ctgaggacaa gtctccactc 3780
cagtaaggga gaggggagga aatgcttctt gtttgaaatg cagtgaattc ctatggctcc 3840
tgtttcacca ccgcaccta tggcaaccca tatacattcc tcttgtctgt aactgccaaa 3900
ggttgggttt atgtcaactc agttccactc aagcattgaa aagggtctca tggagtctgg 3960
ggtgtgcccc gtgaaaagat ggggactttt tcattatcca cagacctctc tatacctgct 4020
ttgcaaaaat tataatggag taactatttt taaagcttat ttttcaattc ataagaaaaa 4080
gacatttatt ttcaatcaaa tggatgatgt ctcttatccc ttatccctca atgtttgctt 4140
gaatttttgt tgttccctat acctactccc taattcttta gttccttctt gtcagggtcc 4200
cttcatttgt actttggagt ttttctcatg taaatttgta taatggaaaa tattgttcag 4260
tttggataga aagcatggag aaataataa aaaaagatag ctgg 4304

```

<210> 104

<211> 3673

<212> DNA

<213> Mus musculus

<400> 104

```

tgctctctgt actaatgtgt ttatggctat ttcccacctt ctctctatg caattttattg 60
tatatggctt tatgttgaag tcttctatcc actttgactt gaaaattgtg cagggtgata 120

```

WO 2005/005597

PCT/US2003/027106

aaaatggatc tgttttcttt ttttctgcat gcagacatca gttaagtcag tatcatttgt	180
tgaagatggt ttcatattgtc cattgtatgg ttttgtcttc catgtcaaat tcaagagtcc	240
ataagtggtt ggggtttattt tgggttcttc aattttattt cattgatcaa catatctggt	300
tctgaacca attccatgca gtttttatca ctatttctct gtattacagt gtgaggtcag	360
ggatgatgat tgcttcacaa gtttttattt atttgtttgt ttgtttttgt ttgtttattt	420
tctgttcttt tgattagaat tgtttgactc tctgtgagc tttttttttt tttttttaat	480
ttcatgtga agttgagaat ggctctaaac atttgtgttg gagttttgct gaggattgca	540
ttgaatctgt ctcttgcttt tggtaagcaa tctactatgt tcttcttact aatctaggag	600
catggggagt ctttccatat tctgataact ctttcaattt ctttcttcaa agacttgaag	660
ttattttgca tagagttctt tcacttactt ggtagagtt acaccaatat attttgtatt	720
acctgtggct attgtgaagg gtatcttttt ccctaatttc tttctctgcc cctctatcat	780
ttgtataaag gagtagaact gttttctatg atttaatttt gtatctaaca acgtcttgty	840
agccattctt gggctcagct ccagtgccac agagtattcc ttgctaaaga tggcatttcc	900
agtgtctct gacttttagc ttggagtta gctccacact accttgatct cttctcaagc	960
ctttcttttg ttttgttttt agcagaactt agttctttcc atgtgcagat ctgtctatat	1020
gtagcaaata aaatctcgga tggattatct tttagttttt agcagttgat ttttgttttc	1080
ttttcatctt aatttctttc atgtaactct gatccattat ttttagaaac tttgcaaaat	1140
actctatttt gttcatttgc aatcacaaat tattgatatt gcttataata gtcagttgta	1200
ctggggaggag aagcttatcat attaaaatat actaaaatat tttatcatta aattttatca	1260
tacacacac acgtgcgtga gcacgcacac acacgcacac acacacacac acacacacac	1320
acacacacac acacacctat tgaggtaaga tgtcataatt ttcttggtgt tcactgtata	1380
ggcaggacta gctttggctt cttatctctc ttcaatcttc tgagtagttg gaactaaagg	1440
tgtgtacctc caagccatgt tatattgctt caattttctt tcccactggt actagtgaat	1500
agagactttg ttgtccattt cattctttta attttgagga attaataagg atttcttttt	1560
atttgaaaca aattaattca acagtttctc atttttctta gagaaaaa agcccttact	1620
gtctggcttc tctgtcgcca cctatctctc tcagcttctg tctccacac aaatctgttt	1680
gtagggaagt agactttgta tttctgtga tgcagtttaa tctctcattt tactcagatt	1740

WO 2005/005597

PCT/US2003/027106

ctttctgaat atattccagt ttagcagccc acactaaacc tggaaatttat gctttgactt	1800
cctcaccaga gatgaaatgc ctttaggaat caggttcagga aacaacattc tggtaggaag	1860
tgtgaaaagg ttcataatt tctacaaaa gagaatggaa gacatgctgg tgttgaccag	1920
ccttgatca tatgttcata tgacttttca aaacagtat tttcttttgg gttgttcttg	1980
tcttccotaa gggagtcctc agaagatgag ttatgtttgg ctattagcag ttcagaattc	2040
ataatatatt attagaatat catctgaagt aatttttgca caagtagtta aagtaagtgc	2100
ttttataaga ccagcgagca tcttgtcag gaatattaca gctctcttcc cacagattct	2160
attggcaatc tctgttttgg tgaggaaatg catgatatat taagcttttt gtgagtttta	2220
aaaacctctt atttctact tagcacattt acatgatata ataaaaagtg gatttttttt	2280
tctgatacat gaattaccat ttatagtgat gcaagctaa ttaccacact tcttctctgc	2340
agggattttg agtgtcaggg tggagaatag accattactg agatttcttt tcttttgttt	2400
tattttttac atggctaagg atgcgggtct aagaagatat ttctatagtc ctttttagga	2460
tacttctctt gatagtagt tgacgttggc ttgaaagtaa cttatctga ggaacaatct	2520
gtacagagcc atgggaagaca tccctaattc cctgaataga agagaagaca aacaaaggaa	2580
aacaaaactt ctcaccctc tgccttttcta taaatttgtc tttgttatta gtccatcttt	2640
gtgattgtca ggctatgaag actgtgacta tcatactgtt gtttggcagc aagtatctaa	2700
attataagaa cagaaacaag ggatatgcca gactccaatg tttgtagcca gttatttctt	2760
ggcatttggt aaaaatatatt ttgcacatac aagatccaaa catactccca tcaaacctgt	2820
gcttgatgtc atataagtct gctaaatctt aattactatg ttttctaact agattcatgt	2880
gcttattgtt ccatccataa gctttataat aagtgttggt caaaacattg ggttccatat	2940
gtgtattttg ttatgtactt tgaccataca aattacttca acatttaaaa caaataataca	3000
aataaataaa acaaaatcta cttacttcca aacatgagat ctgatatgtt gtgattaata	3060
tocatagtat ttttccattg gaaagaattg attttccctt ctgcagcata tataagtgc	3120
agttcacttg ttaaccttta ccacatggc tagggtttga tctcttgaaa atatacaaaa	3180
ataaaatata agacaaaaca aaactatca agtagaagt gggcaagaca aaacaatagt	3240
agaaaaagag cccaagagaa accataaggg tcagagtata ttgattcata tactcagtaa	3300
tctcataaga ataataaatt ggaaatgaaa atatcaattc agagaaccaa gtgtggctct	3360

WO 2005/005597

PCT/US2003/027106

```

ttgaaagttc taagcaccat tcataagtct ctttgagctg atatcagctt tgatcatggt 3420
gatgtatagg gccttggtatt attggcatcc tacattttct tgctactatt atttgcctct 3480
actgtttttt gctgcctcct cttccttggt gttcacttag ctctgagagg agggatttga 3540
tggagacatc catttacaac tgatagttcc aagttctcta attctctgtg tgatggctgt 3600
ctacagatct ctaaatttgt tccaatctgc tataggagga agcttctctg atgacagotg 3660
aacaagataa acc 3673

```